



- A Review

## **GLIPIZIDE : SOME ANALYTICAL, CLINICAL AND THERAPEUTIC VISTAS**

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### **ABSTRACT**

Glipizide is a second generation sulphonylurea with promising hypoglycemic activity. It acts by stimulating the release of insulin from  $\beta$ -cells of pancreas. Glipizide is absorbed rapidly, uniformly with good mean oral bioavailability. It offers several advantages such as swift and short action, high potency and also does not accumulate in plasma on repeated oral administration. Safety profile and effectiveness of glipizide has been well documented in commendable number of experimental models and clinical studies. It is generally well tolerated and categorized as Biopharmaceutics Classification System (BCS) class II drug due to poor water solubility and good permeability. Various analytical methods have also been reported for determination of glipizide in biological fluids. The present article provides a comprehensive review on various analytical methodologies, pharmacology, pharmacokinetics, clinical evaluation, toxicology and therapeutic applications of glipizide.

**Key words:** Glipizide, Second generation sulphonylurea, Analytical, Clinical aspects.

### **INTRODUCTION**

Hypoglycemic activity of sulphonylureas was discovered twice by serendipity: first, in France during World War II by Janbon, whose early observations were corroborated by Loubatieres, and subsequently in 1955 by Francke and Fuchs in Germany. In both instances, the investigators were searching for drugs with antimicrobial actions when the hypoglycemic activity was recognized by chance<sup>1</sup>. Sulphonylureas have been used for more than 50 years in treatment of hyperglycemia in patients with type 2 diabetes mellitus<sup>2</sup>. Carbutamide

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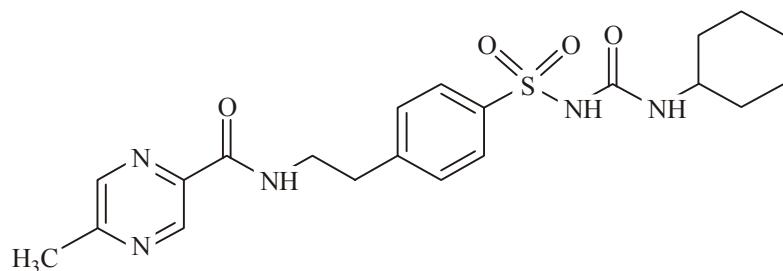
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became the first clinically useful sulphonylurea for treatment of diabetes but it was later withdrawn because of its adverse effects on the bone marrow. This compound led to the development of entirely novel class of oral antidiabetics viz. sulphonylureas. Tolbutamide and chlorpropamide were the first widely used members of this group. Since then, about 12,000 sulphonylureas have been tested<sup>3,4</sup>. The first generation sulfonylureas are still in use, but are less potent than the more recently introduced second generation drugs like gliclazide, glimepiride, glipizide and glibenclamide<sup>5</sup>. An important difference between the older and newer sulfonylureas is a higher specific binding of the latter to pancreatic  $\beta$ -cells. Therefore, the newer sulfonylureas, such as glipizide, are more active<sup>6</sup>. Moreover, second-generation sulfonylureas, which have less electrostatic charges are bound by non-ionic forces; their binding interactions possess a reduced risk of potentiated hypoglycemia as may occur with the first-generation drugs<sup>1</sup>.

Glipizide is one of the most commonly prescribed drugs for treatment of type 2 diabetes mellitus<sup>7</sup>. Its main features are swift and short action with a very high selectivity<sup>8,9</sup>. It is about 100 times more potent than tolbutamide in evoking pancreatic secretion of insulin<sup>10</sup>. Major effect of glipizide is to augment insulin availability following meals, whilst it has little influence on nocturnal glucose control<sup>11</sup>. Glipizide is used for patients with type 2 diabetes who have failed diet and exercise therapy and it appears to be the most effective insulin secretagogue both; in first phase insulin secretion and in sustained stimulatory response during long term administration<sup>12</sup>.

### Physicochemical aspects

Chemically, glipizide is a substituted arylsulphonylurea (Fig. 1). Its empirical formula is  $C_{21}H_{27}N_5O_4S$ , molecular weight is 445.55 and IUPAC name is 1-cyclohexyl-3-[[[p-[2-(5-methylpyrazinecarboxamido)ethyl]phenyl]sulfonyl]urea<sup>13</sup>.



**Fig. 1: Structure of glipizide**

It is white to almost white crystalline, odourless powder prepared by chemical synthesis. It is practically insoluble in water and alcohol; very slightly soluble in acetone and

dichloromethane. It is readily soluble in dilute solutions of alkali hydroxides as well as in dimethylformamide (DMF) and it is also soluble in chloroform and methylene chloride<sup>13-15</sup>. It is a weak acid with pK<sub>a</sub> of 5.9<sup>16</sup>. Its melting range is 208-209°C (crystals from ethanol), however, melting range is also reported as 200-203°C<sup>17</sup>.

### Analytical methodologies

Various analytical methodologies have been reported for quantification of serum level of glipizide, pharmacokinetic evaluation, diagnosing drug abuse or overdose, determining drug-drug protein binding interactions, routine analysis, quality control and stability assurance of drug in pure form and in pharmaceutical preparations; analytical techniques for simultaneous estimation of various antidiabetic drugs have also been developed. Important analytical methodologies employed for glipizide and reported in scientific literature are summarized as below:

A simple, sensitive radioimmunoassay for the direct determination of glipizide in human plasma was developed by Maggi *et al.*<sup>18</sup>, which could measure even small amounts as 1 ng/mL, without extraction or separative procedures. The high sensitivity of this method requires only very small blood samples, and plasma glipizide content can be detected even after a long time of ingestion.

A sensitive and selective high-performance liquid chromatographic (HPLC) method for determination of intact glipizide in human plasma or urine has been developed by Emilsson *et al.*<sup>19</sup> The detection limit of method was reported to be 5-10 ng/mL in plasma or urine. No interferences from metabolites or endogenous constituents were observed. Later, Sener *et al.*<sup>20</sup> reported that this technique could also be employed to study the pharmacokinetics of hypoglycemic sulphonylureas including glipizide, for blood drug monitoring in diabetic patients, for diagnostic purposes in factitious hypoglycemia and in cases relevant to forensic medicine.

Strausbauch *et al.*<sup>21</sup> proposed solid-phase extraction-capillary electrophoresis (SPE-CE) for concentration and separation of hypoglycemic drugs. In this technique, very dilute analytes may be selectively extracted from a sample matrix and concentrated on-line for analysis. They reported that SPE-CE not only increases the sensitivity for detection but that selectivity may be altered due to chromatographic processes occurring on the solid-phase resin. SPE-CE appeared to be effective for the analysis of hypoglycemic drugs in low ng/mL range.

A highly precise, accurate and sensitive liquid chromatography/mass spectrometry

(LC/MS) method for analysis of sulphonylureas including glipizide was introduced by Susanto and Reinauer<sup>22</sup>. This method allows screening of sulphonylureas in serum and subsequently the quantification of the serum level in one run of measurement. It is based on the separation of drugs by HPLC and their identification by mass spectrometry using atmospheric-pressure chemical-ionization and quantification with selected ion monitoring.

Micellar electrokinetic chromatography (MEKC) in tandem with diode array detection (DAD) has been reported as an analytical method for the separation and detection of sulfonylurea drugs by Roche *et al.*<sup>23</sup> They suggested that MEKC with scanning DAD can be used for identifying the presence of metabolites of glipizide and glyburide in the urine of hyperglycemic patients and also as a means of diagnosing sulfonylurea drug abuse.

Naglaa and Kousy<sup>24</sup> proposed stability-indicating densitometric methods for determination of glipizide and other antidiabetic drugs in dosage forms using thin layer chromatography (TLC). The proposed methods, being stability-indicating, accurate, specific and of high precision could be recommended for the routine analysis, quality control and stability assurance of the investigated drugs in pure form as well as in dosage forms.

Aruna and Nancey<sup>25</sup> developed two simple and reproducible spectrophotometric methods for simultaneous estimation of metformin and glipizide in combined dosage forms. The first method employs formation and solving of simultaneous equations using wavelengths of 232 nm and 274 nm whereas second method employs second derivative spectroscopy.

An atmospheric pressure chemical ionization liquid chromatographic–mass spectrometric assay was reported for fast and reliable screening and identification as well as precise and sensitive quantification of oral antidiabetics of the sulfonylurea-type in plasma by Maurer *et al.*<sup>2</sup>

In order to investigate drug–drug protein binding interaction between glipizide and rosiglitazone, a method was developed by Zhongping *et al.*<sup>26</sup> for simultaneously determining the free (unbound) fraction of glipizide and rosiglitazone in plasma employing equilibrium dialysis for the separation of free drug and liquid chromatography–tandem mass spectrometry (LC–MS/MS) for quantitation. No binding interaction was observed between glipizide and rosiglitazone in this study. Emmie *et al.*<sup>27</sup> have also suggested that LC-MS/MS could be used for separation and simultaneous detection of ten antidiabetic drugs including glipizide in equine plasma and urine.

HPLC-UV method utilizing optimized gradient elution with single wavelength

monitoring has been developed for simultaneous determination of six antidiabetic drugs viz. glibenclamide, gliclazide, glipizide, pioglitazone, repaglinide and rosiglitazone in pharmaceutical formulations by Venkatesh *et al.*<sup>28</sup> The method is simple, selective and can be extended for routine analysis of antidiabetics in pharmaceutical preparations and in biological matrices.

A fully validated, simple, fast, sensitive and precise squarewave adsorptive cathodic stripping voltammetric procedure was described for quantification of glipizide in bulk form and in its pharmaceutical formulation without interference from excipients by Ghoniem *et al.*<sup>29</sup>

A rapid and sensitive LC-MS/MS method was developed for the simultaneous quantification of metformin and glipizide in human plasma by Ding *et al.*<sup>30</sup> The method exhibits high efficiency and convenience due to simple sample preparation procedure and optimized LC-MS/MS conditions.

Various analytical methods like radioimmunoassay, HPLC, capillary electrophoresis, LC/MS, MEKC, TLC, LC-MS/MS, UV etc. have been successfully developed and utilized for the estimation of glipizide. These methods have enabled the scientific community to have a close look on various aspects of glipizide such as bioavailability, drug interactions, pharmacological profile, biochemical analysis, forensic investigation etc. so as to optimize its applications through diverse pharmacokinetic/pharmacodynamic approaches.

### Mode of action

Glipizide lowers blood glucose by evoking the release of insulin from the pancreatic  $\beta$ -cells<sup>8</sup>. Like other sulphonylureas, it interacts with receptors on pancreatic  $\beta$ -cells and block adenosine triphosphate sensitive potassium channels. This in turn leads to opening of voltage sensitive calcium channels which produce an influx of calcium ions, calcium-calmodulin binding, kinase activation and release of insulin containing granules by exocytosis<sup>3, 31</sup>.

Other proposed mechanisms include: increase in the sensitivity of peripheral tissues to insulin effects, increase in the number of insulin receptors and increased binding to and/or affinity of insulin for its receptors<sup>32-35</sup>. Extrapancreatic effects may also play key role in therapeutic actions of oral sulphonylurea hypoglycemic drugs. In case of glipizide, two important extrapancreatic effects are – an increase in insulin sensitivity and a decrease in hepatic glucose production<sup>13</sup>. Glipizide also increases the plasma insulin level by reducing metabolic clearance rate of insulin<sup>36</sup>. It has also been reported that it acts by reducing

intestinal glucose absorption, possibly by stimulation of somatostatin release<sup>37</sup>. In addition to its direct insulin-releasing effect, glipizide therapy improves  $\beta$ -cell function secondarily as a consequence of reduced hyperglycemia<sup>38</sup>. Glipizide also shows secondary effects on blood lipids and platelets<sup>8</sup>. It has a mild diuretic action as well<sup>31</sup>.

### Clinical studies

Glipizide is currently used for the treatment of type 2 diabetes mellitus. Important findings from different clinical/pharmacological studies have been summarized in the following text:

A clinical study was performed by Johannessen and Faberberg<sup>39</sup> on a group of 23 patients, newly diagnosed (12) and severe diabetics (11). Both the groups were treated according to crossover design using initial dose of 5 mg/day glipizide, which was further increased by 5 mg at interval of 4-7 days. Oxidase method using autoanalyser was performed to assay the glucose determination and it was concluded that glipizide is an effective highly potent oral sulphonylurea, which at daily doses of 5-20 mg provides satisfactory control in more than 90% of newly diagnosed diabetic patients.

Masbernard *et al.*<sup>40</sup> carried out studies to check efficacy of glipizide in some most complicated diabetic cases. Thirty-five patients (mean age 60 years) who were diabetics for an average nine years were given regularly controlled treatment for an average of seven months with 2.5 to 20 mg of glipizide daily, the mean dose being almost 10 mg/daily. On the basis of 35 observations, they concluded that glipizide is a potent hypoglycemic drug capable of appreciably improving glycemia. The drug also appeared to enhance the antiprothrombin action of anticoagulants.

Balant *et al.*<sup>41</sup> performed clinical studies to predict the effect of renal insufficiency on pharmacokinetics of glipizide in man. The administration of C<sup>14</sup>-glipizide to two patients with renal insufficiency showed that the metabolism of the drug is independent of kidney function and the rate of disappearance of the unchanged glipizide was approximately same as in normals while the half-life of metabolites was increased to 20 h and even more.

Persson<sup>42</sup> recruited nineteen patients, of whom ten had been previously treated with and failed on other oral antidiabetic drugs in a cross-over trial in order to compare the efficacy of glipizide with placebo in the case of newly diagnosed patients and with previous therapy in established diabetics. Glipizide was found to be more effective than placebo in all cases and provided excellent or good control in eight out of the nine newly diagnosed patients.

In a long-term study by Parodi and Caputo<sup>43</sup>, glipizide resulted in an undiminished therapeutic effect. After the first 18 months, fasting blood glucose values were below 130 mg/dL. It was also found that the mean daily dosage during the fourth year (less than 9 mg per day) was lower than that of the first year (10 mg per day). Glipizide has been well tolerated by all patients.

Feinglos and Lebovitz<sup>44</sup> carried out studies in which all the patients were instructed to use a diet containing 45% carbohydrate, with a caloric value appropriate for their ideal body weight and activity level. The patients were then divided into two groups: one group was treated with diet alone, the other with diet plus glipizide. Results showed that 15 patients receiving glipizide alone were able to reduce their fasting plasma glucose levels within 6 week from a mean value of 240 mg/dL to 120 mg/dL and to significantly improve glucose utilization. Thus, successful glipizide therapy results in a significant improvement in glucose utilization, which is related to changes in both; insulin action and insulin secretion.

Boll *et al.*<sup>45</sup> studied the influence of food intake on the absorption of glipizide in both diabetics and in healthy subjects. It was observed that glipizide caused an increase in plasma insulin and a significant diminution of the rise in blood glucose both during continued fasting and when the drug was taken with the breakfast. They concluded that food intake did not influence the peak concentration, elimination half-life or bioavailability of the drug. However, food intake significantly delayed the absorption of glipizide. Further in 1982, they also studied the effect of increased dosage on efficacy of sulphonylureas. Ten type 2 diabetics were examined during long-term treatment, at two dosage levels, with chlorpropamide once daily and glipizide thrice a day. It was observed that lower dosage of glipizide produced better glucose utilization than chlorpropamide. Moreover, the increased dose of glipizide led to impairment instead of further improvement<sup>46</sup>.

Feinglos and Lebovitz<sup>47</sup> carried out investigation to determine long term safety and efficacy of glipizide. Studies included 30 patients with untreated type 2 diabetes mellitus. The long term investigation of glipizide therapy revealed that this compound is an effective antidiabetic agent in certain patients with non insulin dependent diabetes mellitus (NIDDM) and is well tolerated. Patients who had a prolonged response to glipizide demonstrated increased insulin sensitivity in response to the drug. Furthermore, long term therapy with glipizide in contrast to other sulphonylureas, often results in a sustained increase in glucose stimulated insulin secretion.

In a comprehensive series of 29 clinical studies conducted in the United States, Europe, and Latin America, the effects of glipizide were studied in 554 patients with NIDDM, most of whom had diabetes for at least five years. It was found that a majority of

patients who received glipizide in these studies had a significant reduction in both fasting plasma glucose and 2 h postprandial glucose as compared with baseline values<sup>1</sup>.

Cochet *et al.* studied the effect of glipizide on geriatric patients and observed that the drug was well tolerated by the older patients, one instance of mild hypoglycemia disappeared when the daily dosage was split into two doses<sup>1</sup>.

In the European multiple-center trials with glipizide, Lahon and Mann reported excellent, good, or fair responses in 73% of the patients, with fasting glucose levels reduced to 150 mg/dL or below. Nearly half of those who had failed to respond to other sulfonylureas had a satisfactory response to glipizide<sup>1</sup>.

Groop *et al.*<sup>48</sup> compared the pharmacokinetics and metabolic effects of glipizide and glibenclamide in type 2 diabetics. Results showed that both active treatments reduced postprandial blood glucose concentrations and 24 h urinary glucose excretion to a similar degree, but fasting blood glucose concentrations were slightly lower during glibenclamide treatment. Glibenclamide may enhance insulin sensitivity and reduce nocturnal and fasting blood glucose more effectively than glipizide.

The therapeutic equivalence of once and thrice-daily glipizide was studied by Boll *et al.*<sup>11</sup> Two cross-over studies were carried out in 23 patients with type 2 diabetes, to examine whether glipizide can be given once-daily without loss of therapeutic effects. It was observed that the plasma glipizide after breakfast was higher when the whole dose was taken before breakfast than when it was divided. Thus, it was proved that once-daily dosage of glipizide is at least as effective as thrice daily administration with the third dose given before an early dinner.

Bitzen *et al.*<sup>49</sup> carried out studies on thirty eight subjects, out of which 31 had verified NIDDM while 7 had impaired glucose tolerance. The results showed that the addition of a single 5 mg dose of glipizide reduced the post-prandial blood glucose increase, that was not altered by dietary regulation. The efficacy of glipizide was dependent upon the early systemic availability of the drug, but early systemic availability and efficacy were independent of the extent of blood glucose elevation, at least within a range 6-12 mmol/litre of fasting blood glucose.

Groop *et al.*<sup>50</sup> reported that hyperglycemia may delay the absorption of sulphonylurea agents, probably because it impairs gastric motility and/or gastric emptying. They concluded that with the increase in plasma glucose concentration, there was a dose dependent reduction in the plasma glipizide concentration, which was reduced by 50% at the two highest plasma glucose levels compared with euglycemic level.

Pontiroli *et al.*<sup>51</sup> performed clinical studies on thirty one overweight and obese patients, twelve with NIDDM, nine with impaired glucose tolerance (IGT) and ten with normal glucose tolerance (NGT), each underwent four standard oral glucose tolerance tests (75 g), at one week interval, after administration of placebo or glipizide 30 min before glucose. It was shown that acute administration of the very low dose of glipizide (1.0 to 2.5 mg) was able to improve glucose tolerance in overweight and in obese patients with NGT, IGT and with NIDDM. It was concluded that glipizide may become a useful adjunct to diet and exercise in the long term treatment of obese patients with IGT, to prevent development of NIDDM.

Nagy *et al.*<sup>52</sup> carried out studies in which glipizide, has been shown to have *in vitro* immunosuppressive actions on both; human and rat immune cells, without having significant toxic cellular effects. These actions were observed at pharmacologically therapeutic levels of the circulating drug in humans. Using a separate assay system, glipizide was also shown to inhibit macrophage-mediated cytotoxicity towards rat islet cells. These data support the concept that glipizide affects multiple immune cell types. Studies also suggest that glipizide may inhibit release of interleukin-I or tumour necrosis factor from macrophages, or that this drug may be a free radical scavenger. The observations may be relevant to other studies that suggest glipizide can result in insulin conservation in humans and animals.

Clinical studies were also carried out by Schmitz *et al.*<sup>53</sup> in order to examine whether sulphonylureas influence hyperglycemia-induced glucose disposal and suppression of hepatic glucose production (HGP) in type 2 diabetes mellitus. Glucose-induced suppression of HGP was more pronounced during glipizide treatment. Following glipizide treatment hyperglycemia failed to stimulate glycogen synthase activity. Moreover, glipizide resulted in a significant increase in the immunoreactive abundance of the insulin-regulatable glucose transport protein (GLUT4). In addition, glipizide normalized the activity of glycogen synthase and increased the content of GLUT4 protein in skeletal muscle.

Hosszufulusi *et al.*<sup>54</sup> performed experiments on animals to determine whether glipizide could prevent diabetes in the diabetic prone rats. The results indicated that glipizide can prevent diabetes in these animals. It also decreases the prevalence and severity of islet inflammation even after drug withdrawal and may even dampen autoimmune events leading to diabetes onset.

A comparative single dose bioequivalence study of two brands of glipizide namely sucrazide and minidiab on healthy male volunteers was carried out by Zmeili *et al.*<sup>55</sup> A single dose of each brand was assessed in the study. They reported that pharmacokinetic properties viz.  $C_{max}$ ,  $T_{max}$ , AUC, half-life and elimination constants of these two brands

after oral administration of the single dose (5 mg) were similar with no statistical difference between sucrazide and minidiab. In addition, quality control data (assay, disintegration and dis-solution tests) indicated that both brands passed US and British Pharmacopoeia standards.

Jonsson *et al.*<sup>56</sup> studied the pharmacokinetics and effects of oral glibenclamide and glipizide in Caucasian and Chinese patients with type 2 diabetes. Results showed that the overall glucose lowering effects of glipizide and glibenclamide were similar in the two ethnic groups. However, minor ethnic differences in pharmacodynamics were found. In the case of glipizide  $C_{max}$  and AUC were found to be higher in Chinese.

Mohan *et al.*<sup>57</sup> studied 22 type 2 diabetic patients and reported that glipizide treatment for three years lead to increase in the C-peptide value, suggesting that it may preserve the  $\beta$ -cell function at least up to three years after diagnosis.

Eriksson *et al.*<sup>58</sup> studied the efficacy and long-term effects of glipizide treatment on glucose and insulin metabolism in individuals with impaired glucose tolerance (IGT). It was concluded that short-term treatment with glipizide improves glucose and insulin metabolism in subjects with IGT primarily by improving insulin sensitivity mediated by lowering glucose toxicity, thereby providing rest to the  $\beta$ -cells.

Hsieh *et al.*<sup>59</sup> carried out studies to compare the efficacy and tolerability of a sustained-release glipizide (GSR) formulation with those of immediate-release glipizide (GIR) in Chinese patients with type 2 diabetes mellitus. In this small study, treatment with oral GSR was not significantly different from that of treatment with GIR with respect to short-term (12 weeks) fasting plasma glucose and glycosylated hemoglobin reductions in Chinese adults with type 2 diabetes mellitus.

Nauck *et al.*<sup>60</sup> carried out studies to compare the efficacy and safety of sitagliptin and glipizide in patients with type 2 diabetes and depicting inadequate glycemic control on metformin monotherapy. Results showed that the addition of sitagliptin compared with glipizide provided similar hemoglobin A<sub>1c</sub> lowering efficacy over 52 weeks in patients on ongoing metformin therapy.

Jain *et al.*<sup>61</sup> investigated *in vitro* iontophoretic delivery of glipizide across the pig skin. The experiment was carried out at three different donor drug concentrations using cathodal iontophoresis with corresponding passive controls. At all concentration levels, iontophoresis showed enhanced permeation rate compared to passive controls. Results showed that glipizide is a promising candidate for iontophoretic delivery.

Chung *et al.*<sup>62</sup> carried out pharmacokinetics and pharmacodynamics study of immediate-release glipizide and extended release glipizide GITS (glucotrol XL). It was found that at steady state, the mean  $C_{max}$  after immediate-release glipizide was significantly greater than after glipizide GITS, and the  $t_{max}$  was considerably shorter. Although the mean  $C_{min}$  with glipizide GITS was about 80% higher than with immediate-release glipizide, the mean AUC was significantly lower. Despite the lower plasma concentrations with glipizide GITS in this short-term study, the two formulations were found to have similar effects on serum concentrations of glucose, insulin and C-peptide.

Prasad *et al.*<sup>63</sup> studied the influence of benazepril on glucose lowering effect of glipizide in normal and diabetic rats. Benazepril significantly altered the peak effect and enhanced the hypoglycemic activity in both normal and diabetic animals following treatment for 7 days without any change in onset of action of glipizide. This study suggested that the dose and frequency of glipizide must be readjusted, when it is to be used concomitantly with antihypertensive drug benazepril in combined hypertension and diabetic conditions to avoid severe hypoglycemia due to benazepril.

### Pharmacokinetic aspects

Pharmacokinetic characteristics viz. absorption, distribution, metabolism and elimination of glipizide are summarized here.

#### Absorption

Glipizide is absorbed uniformly, rapidly and completely when given through oral route as an immediate release dosage forms<sup>13, 64</sup>. The absolute bioavailability of glipizide was observed to be about 100% after single oral doses in patients with type 2 diabetes as there is no presystemic metabolic loss<sup>8,13</sup>. The gastrointestinal resorption of glipizide is also almost complete<sup>41</sup>. However, its absorption is erratic in diabetic patients due to impaired gastric motility or gastric emptying. This erratic absorption of glipizide is clinically relevant, since the efficacy of short acting sulphonylureas is dependent on absorption rate of drugs<sup>9</sup>. Exceptional patients may have a slower absorption. The absorption rate is an important determinant of clinical efficacy of this drug<sup>8</sup>.

Food delays absorption of immediate release glipizide by about 40 min<sup>64</sup>. Bitzen *et al.*<sup>49</sup> suggested pre-meal administration of glipizide and proposed that increase in hypoglycemic action of glipizide when it is given 30 min before breakfast is due to the fact that glipizide is more rapidly absorbed when taken with an empty stomach. They also reported that early systemic availability and efficacy of glipizide are independent of the extent of blood glucose elevation atleast within the range of 6-12 mmol/litre of fasting blood

glucose. Administration of glipizide to normal males before high fat meal showed 40% increase in the time to reach peak serum concentration with no significant effect on area under the curve (AUC)<sup>31</sup>.

In case of extended release glipizide, food had no effect on the lag time of absorption<sup>31</sup>. The mean relative bioavailability of glipizide in 21 males with type 2 diabetes after administration of 20 mg glucotrol XL extended release tablets compared to immediate release glucotrol 10 mg given twice daily was 90% at steady state. In the case of glipizide extended release tablets, plasma drug concentration gradually rises reaching maximum concentration within 6-12 h after dosing. Studies also showed that it took approximately 1-2 days longer to reach steady state concentration in 24 elderly type 2 diabetic patients (>65 years)<sup>13</sup>.

Glipizide might undergo enterohepatic circulation to a minor extent allowing the drug to be reabsorbed during meals, this may be more pronounced in patients with reduced hepatic metabolism caused by liver disease<sup>8</sup>.

### Distribution

Glipizide is rapidly distributed and has a small apparent volume of distribution<sup>65</sup>, about 0.14 litre kg<sup>-1</sup> with a range of 0.07-0.19 litre kg<sup>-1</sup>. Protein binding was studied in serum from volunteers who received either oral or intravenous glipizide and found to be 98-99 % one hour after either route of administration<sup>64</sup>. Glipizide mainly binds to albumin proteins<sup>8</sup>.

### Metabolism

The metabolism of glipizide is extensive and occurs mainly in the liver; liver metabolizes the drug mainly into hydroxylated and conjugated derivatives, its two metabolic by-products are *trans*-4-hydroxyglipizide and *cis*-3-hydroxyglipizide; neither metabolite appears to be active<sup>3, 66</sup>. The major metabolites of glipizide are products of aromatic hydroxylation and have no hypoglycemic activity. Minor metabolite, which accounts for less than 2 % of a dose, an acetylaminooethyl benzene derivative, is reported to have 1/10 to 1/3 as much hypoglycemic activity as the parent compound<sup>13</sup>.

### Elimination

Glipizide is eliminated primarily by hepatic biotransformation, less than 10% of a dose is excreted as unchanged drug in urine and faeces; approximately 90% of a dose is excreted as biotransformation products in urine (80%) and faeces (10%)<sup>13</sup>. The half-life of elimination ranges from 2-4 h in normal subjects, whether given intravenously or orally<sup>64</sup>.

However, in initial studies, half-life of drug was reported to be 1.71-2.1 h<sup>67</sup>. The metabolic and excretory patterns are similar with the two routes of administration, indicating that first-pass metabolism is not significant<sup>64</sup>. Studies on renal impaired patients provide information that renal insufficiency does not affect metabolism of drug, only clearance of metabolites from blood is affected<sup>41</sup>. Various pharmacokinetic properties of glipizide are summarized in Table 1.

**Table 1: Pharmacokinetic properties of glipizide<sup>68</sup>**

Pharmacokinetic parameter	Value
Oral absorption	100%
Mean elimination half-life	2-4 h
Pre-systemic metabolism	0%
Minimum effective concentration	20 ng/mL
Maximum effective concentration	300 ng/mL
Plasma protein binding	98-99%

### Toxicology

No sign of carcinogenicity has been shown by administration of large dose i.e. as higher 75 times of the maximum human dose in rats and mice for 20 and 18 months, respectively. Bacterial and *in vivo* mutagenicity tests showed no evidence of mutagenicity. Also, no teratogenicity has been reported to be associated with this drug. Moreover, studies in male and female rats showed no evidence of impaired fertility. But, studies in rats have shown glipizide to be fetotoxic at all doses from 5 to 50 mg/kg; the fetotoxicity is thought to be due to pharmacologic hypoglycemic effect during the perinatal period. It is recommended that if glipizide is used during pregnancy, it should be discontinued at least one month before the expected delivery date<sup>8,31</sup>.

Lower initial doses of sulphonylureas for type 2 diabetes are prescribed to elderly patients because of possible increased sensitivity to this drug due to age related changes in metabolic rate and excretory rate. Generally, short acting glipizide causes fewer problems than other long acting sulphonylureas<sup>31</sup>. Spiller *et al.*<sup>69</sup> performed the prospective observational study of unintentional pediatric sulfonylurea exposures in children of 12 years of age and younger, who were reported to 10 regional poison centers. Out of 56 patients who developed hypoglycemia, 42 exhibited no clinical signs of hypoglycemia. Minor clinical symptoms such as agitation, lethargy were exhibited in the remaining 14 patients. Cases of

delayed onset of hypoglycemia appeared in patients started on a prophylactic intravenous glucose infusion<sup>69</sup>.

Despite approximately 1900 oral hypoglycemic poisonings in children younger than 6 years old per year reported to the American Association of Poison Control Centre, only one death can be ascribed to a sulfonylurea medication in a young child<sup>70</sup>. Szlatenyi *et al.*<sup>71</sup> reported a case of a 2-year-old boy who ingested a single tablet of glipizide 5 mg as well as 25 mg of hydrochlorothiazide. His initial glucose level was >100 mg/dL and he was asymptomatic, but was placed on a glucose infusion treated with activated charcoal. Eleven hours later, he developed asymptomatic hypoglycemia that was treated with oral glucose and an increase of his glucose infusion, and he was eventually discharged without sequelae.

### **Drug interactions**

The pharmacokinetics as well as pharmacodynamic properties of a drug can be altered by previous or concurrent administration of another drug. Some important drug interactions of glipizide with different drugs are summarized here.

Alcohol is reported to prolong but not increase the hypoglycemic effect of glipizide. A disulfiram-like reaction (characterized primarily by flushing of the face, neck and arms) can occur but rarely with sulphonylureas like glipizide, gliclazide, glibenclamide etc.<sup>72,73</sup> Sodium bicarbonate (3 g) significantly increased the absorption of glipizide (5 mg) and enhanced its effects to some extent, but the total absorption was unaltered<sup>74</sup>. Magnesium hydroxide (850 mg) also considerably increased the rate of absorption of glipizide (5 mg)<sup>75</sup>.

Glipizide may significantly increase the plasma concentration of cyclosporine by reducing its metabolism, dose reduction of cyclosporine may be necessary<sup>31</sup>. Studies had also reported that fluconazole induces severe hypoglycemia shortly after concurrent administration of glipizide. There is some evidence that the hypoglycemic effect of glipizide may be modestly increased. Studies showed that when fluconazole 100 mg was given daily for 7 days to person receiving 2.5 mg single doses of glipizide, the AUC was increased by 49% in 13 healthy subjects and their maximum serum level rose by 17%<sup>76</sup>. One case of hypoglycemic coma was reported in the case of diabetic female patient receiving glipizide 2.5 mg thrice daily alongwith 200 mg fluconazole<sup>77</sup>. Posaconazole 400 mg twice daily for 10 days had no significant effects on the steady-state pharmacokinetics of glipizide 10 mg daily, but there was a small significant decrease in blood glucose levels following concurrent use<sup>78</sup>.

Trimethoprim may augment glipizide induced hypoglycemia and patients should be closely observed, when using these drugs simultaneously<sup>79</sup>. One case of acute hypoglycemia

was reported when glipizide was administered with co-trimoxazole<sup>80</sup> while other study indicated no interaction<sup>81</sup>. Isolated cases of severe hypoglycemia in type 2 diabetic patients receiving glipizide and clarithromycin has been reported<sup>82</sup>. Study in 10 healthy subjects found rifampicin 600 mg daily for 5 days decreased the AUC of a single 2.5 mg dose of glipizide given on 6<sup>th</sup> day by 22%. The elimination half-life was shortened from 3 to 1.9 h by rifampicin, but no significant differences in blood glucose concentrations were found<sup>83</sup>.

Colestyramine reduced the absorption of a single 5 mg dose of glipizide in 6 healthy subjects by a mean of 29%. Peak serum levels were reduced by 33% when the two were taken simultaneously<sup>84</sup>. In a study, patients with type 2 diabetes were given 400 mg cimetidine 1 h before taking a dose of glipizide and then 3 h later, they were given a standard meal with cimetidine 200 mg. The expected rise in blood sugar levels after the meal was reduced by 40% and in some of the patients, it fell to less than 3 mmol/L<sup>85,86</sup>. In another studies involving patients with type 2 diabetes, it was found that ranitidine 150 mg or 300 mg had no significant effects on the pharmacokinetics or the effects of glipizide, except that the absorption was delayed<sup>87,88</sup>.

Fasting blood glucose values decreased in 10, and increased in 4 of 14 diabetic patients on glipizide who were given gemfibrozil, 800 mg daily initially, reduced later to 400 to 600 mg daily<sup>89</sup>. In a study on 6 healthy subjects, it was found that serum glipizide level rose and blood sugar level reduced when they took indobufen 200 mg as a single dose and then twice daily for a 5 day period<sup>90</sup>. However, no important change in blood sugar levels occurred in 24 type 2 diabetics on glipizide when they took indoprofen 600 mg daily for 5 days<sup>91</sup>. A study found that although indoprofen lowered the plasma levels of a single 5 mg dose of glipizide, the blood sugar levels remained unaffected<sup>92</sup>.

A diabetic, treated for 6 months with glipizide 5 mg daily experienced recurring episodes of hypoglycemia over a period of 4 days, after taking a routine 5 mg dose of glipizide, possibly due to interaction with heparin<sup>93</sup>. Food delays the absorption and thus reduces the effect of glipizide, when it is administrated along with the drug<sup>8</sup>. One year clinical trial on 139 patients taking orlistat and glipizide showed that 43% obese patients with type 2 diabetes were able to decrease their sulphonylurea dosage and 11.7% of them were able to discontinue the sulphonylurea<sup>94</sup>. The interactions of glipizide with various drugs are summarized in Table 2.

### **Adverse effects /contraindications**

Glipizide is the most popular sulphonylurea, however, some adverse effects have been reported. Gastrointestinal effects like diarrhea, nausea, gastralgia and skin reactions

have been reported in a low frequency (1-3%)<sup>95</sup>. Glipizide extended release tablets treated patients reported some incidence of side effects such as asthenia, headache, dizziness, nervousnesss, tremor, diarrhea and flatulence<sup>13</sup>. Severe allergic skin reactions; rashes; pruritus; erythema; sunburns; photosensitivity were also reported to occur<sup>96</sup>.

Glipizide is contraindicated in patients with known hypersensitivity to this drug. It is contraindicated in type 1 diabetes mellitus<sup>13</sup>. Glipizide should be avoided in hepatic impairment, diabetic ketoacidosis with or without coma<sup>8</sup>. It is also contraindicated in pregnant women<sup>97</sup>.

**Table 2: Drug interactions of glipizide with different drugs<sup>31,73-84</sup>**

Interactant	Interaction effect
Alcohol	Prolong hypoglycemic effect of glipizide
Sodium bicarbonate	Increased rate of absorption of glipizide
Magnesium hydroxide	Increased rate of absorption of glipizide
Cyclosporine	Glipizide reduces metabolism of cyclosporine
Fluconazole	Severe hypoglycemia
Posaconazole	Severe hypoglycemia
Ranitidine	Delayed absorption of glipizide
Gemfibrogil	Fasting blood glucose values decreased
Trimethoprim	Hypoglycemia
Co-trimoxazole	Hypoglycemia
Indobufen	Lowering of plasma level of glipizide
Clarithromycin	Severe hypoglycemia
Rifampicin	Elimination half-life of glipizide reduced
Heparin	Hypoglycemia
Colestyramine	Reduced absorption of glipizide

### Dosage

The recommended dose range is 2.5-20 mg daily. The highest therapeutic dose of glipizide known to have been used is 40 mg daily<sup>98</sup>. When patients are transferred to

glipizide from another sulphonylurea antidiabetic preparation (exception of chlorpropamide), no transition period is required. During conversion from insulin therapy to glipizide therapy, no gradual dosage adjustment usually is required for patients using less than 20 USP units of insulin daily. For patients using 20 or more USP units daily, a 50% reduction of insulin the first day, with gradual dosage adjustments of glipizide as needed is desirable<sup>31</sup>.

## CONCLUSION

Although glipizide is a relatively old drug, yet it is still a very effective and clinically significant hypoglycemic agent. Since its introduction in early 1970s, lots of clinical studies have been done which prove that the drug is a potent insulin secretagogue, both in first-phase insulin secretion and in the sustained stimulatory response during long term administration. Also, significant number of reports have been published on the quantitative estimation of drug in the biological fluids employing various analytical methodologies. Hence, it can be concluded that glipizide, being an effective, time tested and promising oral hypoglycemic agent seems to hold its pivotal position in antidiabetic therapy.

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