Bioavailability File: Glipizide

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Summary

Glipizide is a member of the second-generation sulfonylurea drugs used in the treatment of type 2 diabetes mellitus. It is completely absorbed from the gastrointestinal tract and metabolized into five different metabolites in the liver, and does not show the hypoglycemic activity by itself. It exhibits its hypoglycemic activity through pancreatic and extrapancreatic pathways. Glipizide is 98% bound to plasma proteins and has a half-life between 2.5 and 4.7 hours. Cimetidine and ranitidine increase the plasma concentration of Glipizide approximately three times. On the other hand, active charcoal may decrease the absorption of Glipizide. No effect of age or obesity exists on the absorption and bioavailability of Glipizide. In this paper, the physicochemical and pharmacological properties, determination methods and pharmacokinetics of Glipizide are reviewed.

Key Words: Glipizide, NIDDM, type II diabetes, pharmacokinetics, bioavailability.

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INTRODUCTION

Non-insulin dependent diabetes mellitus (NIDDM) (type II diabetes) is a disorder characterized by an increase in hepatic glucose production and destruction of peripheral glucose intake1. The most common drugs prescribed for the stimulation of insulin release are the sulfonylureas2. Glipizide is a member of the second-generation sulfonylureas firstly synthetized in Italy in 19713. The hypoglycemic activity is nearly 100 times greater than of those belonging to the first generation of sulfonylureas. In 1984, with Glyburide, the manufacturers submitted this drug to the Food and Drug Administration (FDA) and it has been on the market for more than 20 years4. It is well tolerated and no important side effect has been reported.

Physicochemical Properties

Glipizide was firstly synthesized in 1971 by Ambrogi et al.5-7, and belongs to the second-generation sulfonylurea drugs8,9. It was derivatized by the addition of a cyclohexyl group to the main structure of sulfonylurea and substitution of a non-polar group to the phenyl circle3. The chemical structure is 1-cyclohexyl-3-[[p-2-(5-methylpyrazinecarboxamido) ethyl]...
phenyl sulfonyl] urea. The molecular formula of Glipizide is \( \text{C}_{21}\text{H}_{27}\text{N}_{5}\text{O}_{4}\text{S} \) (Fig. 1) with the molecular weight 445.54 g/mol.

Glipizide is a white odorless crystalline powder with a melting point at 208\(^\circ\)C-209\(^\circ\)C. It is insoluble in water and alcohol, and slightly soluble in acetone. On the other hand, it is soluble in methylene chloride, chloroform, freely soluble in dilute alkali hydroxides, and dimethyl formamide. It is 98% bound to plasma proteins and has a pKa=5.9, making it a weak acidic drug.

**Identification and Quantification Methods**

Since Glipizide is used at very low doses, highly sensitive methods for the determination of Glipizide have been investigated in the literature. For the determination of Glipizide from plasma and pharmaceutical dosage forms, high pressure liquid chromatography (HPLC), thin layer chromatography (TLC), liquid chromatography (LC), capillary electrophoresis, radioimmunoassay, and UV spectrophotometry have been previously evaluated. The sensitivity of HPLC was 5 ng/ml and Lin et al. developed a liquid chromatography-mass spectrometry (LC-MS) method with a lower limit of quantification (LLOQ) of 1 ng/ml.

Glipizide has the maximum absorbancy at \( \lambda=276\text{ nm} \) (aqueous acid). The effects of pH and surfactants on the dissolution properties of Glipizide were investigated by Jamzad et al. by using UV spectrophotometry. The same determination method was also used for the investigation of release characteristics of Glipizide from pellet formulations, matrix tablets, osmotic tablets with cyclodextrins, and mucoadhesive microspheres. On the other hand, the release of Glipizide from lipospheres has been characterized by UV spectrophotometer at \( \lambda=223\text{ nm} \) by Shivakumar et al.

Becker et al. used HPLC method equipped with a fluorometric detector for the quantification of Glipizide. Feely et al. used the same method for the determination of Glipizide from plasma with tolbutamide as the internal standard. For the determination of Glipizide from breast milk, Feig et al. evaluated an HPLC method with fluorometric detection (excitation=470 nm, emission=530 nm) with limit of detection (LOD) 0.005 \( \mu\)g/ml.

The determination of Glipizide from plasma has been evaluated by using a HPLC method by Wahlin-Boll et al., and many researchers have used the same method with some slight modifications. The determination of Glipizide from plasma after administration of its combined dosage forms with metformin has been done again by using HPLC-UV method (\( \lambda=225\text{ nm} \)) following a solid phase extraction technique. The LOD and LOQ of this method were 4.5 ng/ml and 7.5 ng/ml, respectively. The determination of Glipizide with six other anti-diabetic drugs from pharmaceutical dosage forms and plasma has been investigated with suitable gradient systems with the same HPLC-UV method (\( \lambda=260\text{ nm} \)). No extraction method has been used for the pharmaceutical dosage forms, but on the other hand, a simple extraction with acetonitrile has been employed for the plasma samples.

Maggi et al. used the radioimmunoassay method for the determination of Glipizide from plasma. This method was also used in another study by Huupponen et al. in which they have investigated the effect of guar gum on the bioavailability of Glipizide in humans.

For the determination of unbound Glipizide in plasma, a LC-tandem mass spectrometry (LC-MS-MS) method was investigated. Samples of 0.2 ml were extracted and analyzed with high pressure liquid chromatography-tandem mass spectrometry (m/z 446/321) with...
an LOD of 1 ng/ml\textsuperscript{27}. Ho et al.\textsuperscript{26} investigated another LC-MS (m/z 321) method for the determination of Glipizide in plasma and urine samples in horses and the LOD of this method was found as 1 ng/ml. These two methods involve extraction procedures. Because of the long retention time (20 min) of Glipizide, Ding et al.\textsuperscript{28} developed a new LC-MS/MS analysis method. In this method, organic solvent was added to plasma samples in order to precipitate the proteins and the retention time was 2 min for Glipizide. The LLOQ of this new method was found as 0.004 µg/ml.

**Pharmacology**

**Mechanism of Action**

The major pharmacological effects of the drug substances belonging to the class of sulfonylureas may be classified as extra pancreatic and pancreatic activities and the modification of the other systems\textsuperscript{3}. The mechanism of action of Glipizide is given in Table 150.

**Table 1.** The hypoglycemic activity mechanisms of Glipizide\textsuperscript{50}

<table>
<thead>
<tr>
<th>Site of action</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic activity</td>
<td>Regulation of insulin release</td>
</tr>
<tr>
<td></td>
<td>Decrease glucagon secretion</td>
</tr>
<tr>
<td>Extrapancreatic activity</td>
<td>Regulation of the sensitivity of the tissue to insulin</td>
</tr>
<tr>
<td>Direct</td>
<td>Increase receptor binding</td>
</tr>
<tr>
<td></td>
<td>Regulation of activity following binding</td>
</tr>
<tr>
<td>Indirect</td>
<td>Regulation of hyperglycemia</td>
</tr>
<tr>
<td></td>
<td>Decrease the concentration of the plasma free fatty acids</td>
</tr>
<tr>
<td></td>
<td>Decrease the hepatic insulin secretion</td>
</tr>
</tbody>
</table>

**Pancreatic activity**

Many studies reveal that drugs belonging to the class of sulfonylureas stimulate the secretion of insulin from the pancreatic beta cells existing in the liver\textsuperscript{7,51-53}. The intrinsic insulin release capacity of Glipizide is 100 times more than that of the first generation sulfonylureas\textsuperscript{54-57}. In the rat pancreas perfusion study by Artini et al.\textsuperscript{56}, the tissues were separately perfused with Glipizide and Glyburide for 15 min. Insulin release was immediately achieved with Glipizide and reached a maximum level in 5 min (Fig. 2). Twenty minutes after the end of perfusion with Glipizide, the level of insulin returned to its basal level. In another study, by Barr et al.\textsuperscript{58}, dogs were randomly allocated into three groups as follows: Group 1: 80% proximal pancreatectomy; Group 2: Proximal pancreatectomy plus splenocaval diversion; Group 3: Control. After administration of Glipizide (5 mg, oral, twice daily), no effects on insulin secretion after the loss of beta cell amount and glucose handling were found. Although Glipizide’s exact mechanism of action in affecting the release of insulin from beta cells is unknown, it is a common thought that due to the changes in the cellular flux of sodium and calcium ions, specific binding to the cellular membrane is responsible\textsuperscript{59,60}. Glipizide shows its effect by increasing the sensitivity of beta cells in the liver to glucose. Hence, insulin release but not insulin synthesis is increased in all glucose levels\textsuperscript{61}. Marco et al.\textsuperscript{62} found no difference in glucagon secretion after a seven-day administration of Glipizide to healthy volunteers.

**Extrapancreatic activity**

The extrapancreatic activity of the sulfonylurea drugs has been investigated by many researchers\textsuperscript{63-65}. In healthy animals and diabetic patients, the extrapan-
cretic as well as pancreatic activity of Glipizide has been evaluated. These effects increase the peripheral and hepatic activity of endogenous and exogenous insulin. A statistical difference in hypoglycemia was investigated between two groups of animals, with the first group receiving low-dose Glipizide and the second receiving low-dose insulin as the control group. In addition, insulin receptors in the hepatic plasma membrane increased 2.5 times more with respect to the control group. NIDDM patients treated with Glipizide showed increased responses to insulin, increased peripheral glucose uptake and suppression of hepatic glucose production.

**Uses and Administration**

Most of the patients with NIDDM are treated with 5-20 mg/day Glipizide administration. It is recommended for 15 mg/day patients to take the drug 30 min before breakfast and for >15 mg/day patients to take the first portion as half of the total dose 30 min before breakfast and second portion 30 min before dinner. The blood glucose level must be monitored carefully in patients crossing over the insulin therapy to the Glipizide therapy. Low-dose of insulin (<20 U/d) may be exchanged with 5 to 10 mg/day Glipizide. If there is a problem with insulin treatment or if patients with NIDDM can be well controlled with Glipizide, insulin treatment should be replaced by Glipizide treatment.

**Side Effects**

Although many studies indicate that Glipizide is side-effect free, some researchers have reported certain side effects, including some gastrointestinal side effects such as diarrhea, vomiting, nausea and abdominal pain, some skin reaction characterized by rashes and alcohol-induced flushing and hypoglycemia.

**Pharmacokinetics and Bioavailability**

**Absorption**

Glipizide is completely and rapidly absorbed from the gastrointestinal channel. The maximum plasma concentration is reached after 1.2-3.5 hours following oral administration. The plasma concentration was found to be in a range of 540-1644 nmol/L and the mean plasma concentration was calculated as 1020 and 1093 nmol/L. After high does, such as 0.1 mg/kg and 10 mg, the mean plasma level was found as 2050 and 2259 nmol/L. The absorption of Glipizide is delayed if it is taken together with food. According to this result, Glipizide must be taken 30 min before meals.

**Figure 3.** Effect of food on the plasma concentration of Glipizide (n=14 NIDDM patients).

**Table 2.** The effect of active charcoal and cholestyramine on the absorption of Glipizide.

<table>
<thead>
<tr>
<th></th>
<th><strong>C&lt;sub&gt;max&lt;/sub&gt;</strong> (ng/ml)</th>
<th><strong>t&lt;sub&gt;max&lt;/sub&gt;</strong> (h)</th>
<th><strong>AUC&lt;sub&gt;(0-10h)&lt;/sub&gt;</strong> (ng.h/ml)</th>
<th>Relative Bioavailability (% of control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>425±36</td>
<td>1.3±0.33</td>
<td>1830±267</td>
<td>100</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>285±31&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.9±0.41</td>
<td>1260±145&lt;sup&gt;a&lt;/sup&gt;</td>
<td>71 (59-83)</td>
</tr>
<tr>
<td>Charcoal</td>
<td>89±31&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.0±0.22</td>
<td>352±128&lt;sup&gt;a&lt;/sup&gt;</td>
<td>19 (8-37)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Significantly different (p<0.01) from control group (Student’s paired t-test, two-tailed) n=6 mean±s.e.
Table 3. Effect of sodium bicarbonate (3.0 g)\textsuperscript{45}, aluminium hydroxide (1.0 g)\textsuperscript{45} and magnesium hydroxide (0.85 g)\textsuperscript{17} on the pharmacokinetics of Glipizide (5 mg)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>NaHCO\textsubscript{3}</th>
<th>Control</th>
<th>Al(OH)\textsubscript{3}</th>
<th>Control</th>
<th>Mg(OH)\textsubscript{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>t\textsubscript{max} (h)</td>
<td>2.5±0.22</td>
<td>1.0±0.21\textsuperscript{a}</td>
<td>2.3±0.18</td>
<td>2.4±0.32</td>
<td>1.6±0.32</td>
<td>1.2±0.29</td>
</tr>
<tr>
<td>t\textsubscript{1/2 absorption} (h)</td>
<td>1.24±0.25</td>
<td>0.27±0.09\textsuperscript{a}</td>
<td>0.94±0.18</td>
<td>1.3±0.28</td>
<td>0.32±0.06</td>
<td>0.15±0.02\textsuperscript{b}</td>
</tr>
<tr>
<td>Lag time (h)</td>
<td>0.28±0.03</td>
<td>0.22±0.01\textsuperscript{b}</td>
<td>0.30±0.03</td>
<td>0.31±0.06</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C\textsubscript{max} (ng/ml)</td>
<td>497±75.2</td>
<td>613±24.4\textsuperscript{b}</td>
<td>508±58.4</td>
<td>451±21.3</td>
<td>416±26.7</td>
<td>445±32.0</td>
</tr>
<tr>
<td>AUC\textsubscript{0-1/2} (ng.h/ml)</td>
<td>122±6.1</td>
<td>78.5±24.4\textsuperscript{b}</td>
<td>10.6±5.4</td>
<td>18.6±8.9</td>
<td>27.0±10.5</td>
<td>75.2±19.4\textsuperscript{b}</td>
</tr>
<tr>
<td>AUC\textsubscript{0-1} (ng.h/ml)</td>
<td>73.1±20.7</td>
<td>316±42.7\textsuperscript{a}</td>
<td>69.6±17.6</td>
<td>88.5±32.9</td>
<td>155±40.4</td>
<td>262±36.9\textsuperscript{b}</td>
</tr>
<tr>
<td>AUC\textsubscript{0-2} (ng.h/ml)</td>
<td>346±111</td>
<td>837±87.5\textsuperscript{a}</td>
<td>387±82.9</td>
<td>341±81.7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AUC\textsubscript{0-10} (ng.h/ml)</td>
<td>2330±393</td>
<td>2490±443</td>
<td>2230±347</td>
<td>2041±268</td>
<td>1665±198</td>
<td>1718±167</td>
</tr>
<tr>
<td>AUC (ng.h/ml)</td>
<td>3540±922</td>
<td>3240±841</td>
<td>3250±832</td>
<td>2730±629</td>
<td>2048±383</td>
<td>2025±300</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>8.3±2.0</td>
<td>6.1±1.7\textsuperscript{a}</td>
<td>7.3±1.8</td>
<td>6.4±1.1</td>
<td>5.6±0.85</td>
<td>4.9±0.57</td>
</tr>
<tr>
<td>t\textsubscript{1/2} (h)</td>
<td>4.8±1.4</td>
<td>4.2±1.6</td>
<td>4.2±1.3</td>
<td>3.2±0.66</td>
<td>3.4±0.7</td>
<td>3.1±0.35</td>
</tr>
</tbody>
</table>

\textsuperscript{a} P<0.01 \textsuperscript{b} P<0.05 compared to control.

Kivistö et al.\textsuperscript{17,45} investigated the possible effects of antacid drugs (NaHCO\textsubscript{3}, Al(OH)\textsubscript{3}, Mg(OH)\textsubscript{2}) on the absorption and other pharmacokinetic parameters of Glipizide (Fig. 4) (Table 3). No effect of aluminum hydroxide on the absorption of Glipizide was found, whereas sodium bicarbonate and magnesium hydroxide accelerated the absorption of Glipizide as well as the effect of Glipizide on glucose level.

The plasma concentration of Glipizide is increased when it is used in combination with H2 receptor antagonists such as ranitidine and cimetidine. Cimetidine and ranitidine increased AUC values of Glipizide from 2267±387 ng.h/ml to 2792±704 ng.h/ml and from 2947±508 ng.h/ml to 3953±601 ng.h/ml, respectively (P<0.05). No differences in the elimination half-life and protein binding were observed\textsuperscript{21}. The absorption of Glipizide was delayed (AUC=5251±1383nmol.h/L to 6547±980nmol.h/L, P<0.05) and elimination half-life of Glipizide insignificantly prolonged (t\textsubscript{1/2}=2.8±0.5h to 3.3±0.5h, NS) when combined with indobufen, a nonsteroidal anti-inflammatory drug\textsuperscript{87}.

In another study investigating the effect of age, diabetes, and multiple dosing regimens on Glipizide pharmacokinetics, no changes in t\textsubscript{max}, C\textsubscript{max}, AUC, CI, Vss, Varea, and t\textsubscript{1/2} values were found. On the other hand, in all groups, a statistically significant difference was observed in fp (free fraction of drug)\textsuperscript{43}.

Similar to this result, no effect of obesity was reported by Jaber et al.\textsuperscript{46}. Additionally, guar gum had no harmful effect on the absorption of Glipizide when given either with the drug or half an hour later with breakfast\textsuperscript{31}.

The oral bioavailability of Glipizide increases when the extended release dosage forms are compared with the conventional tablet forms. Elementary osmotic pump (EOP) tablets and bilayered matrix tablets prepared with hydroxypropylmethylcellulose (HPMC) were compared with conventional Glipizide tablets through AUC values obtained from profiles of time versus plasma concentrations of Beagle dogs (Fig. 5). The bioavailability of the EOP tablets were recorded as 102.8% when compared with conventional tablet dosage forms\textsuperscript{88}.

The C\textsubscript{max} and AUC values of Glipizide are three times more than those of glibenclamide, which is also another member of the sulfonylurea drugs (Table 4, Fig. 6)\textsuperscript{41}.

**Distribution**

The volume of distribution of Glipizide was calculated by the administration of both radiolabelled and unlabelled Glipizide in humans. Three healthy volunteers received oral 5 mg C\textsuperscript{14}-Glipizide and volume of distribution was calculated as 20.4 L\textsuperscript{32}. In two different
studies, the volume of distribution was found as 5.0 L\textsuperscript{89} and 6.7 L\textsuperscript{90} for Glipizide. Schmidt et al.\textsuperscript{83} found volume of distribution as 11.1 L, corresponding to 15% of the total body weight. In rats receiving C\textsuperscript{14}–labeled Glipizide, the total radioactivity was determined in blood and highly perfused organs\textsuperscript{91}.

Pentikainen et al.\textsuperscript{84} calculated the volume of distribution as 12 L and the red blood cellular uptake of Glipizide as very low levels. For the use of Glipizide in breastfeeding mothers, conventional tablet dosage forms were administered and no drug was determined in the milk, so it was concluded that mothers may safely use Glipizide during this period\textsuperscript{40}.

**Metabolism and Elimination**

The half-life of Glipizide is very short (2.5-4.7 hours)
when compared with the other drugs in the sulfonylurea group. Although not in all of the studies, the calculations were investigated according to the two compartmental models. Glipizide is mainly metabolized in the liver. Five percent of the total dose is introduced to the first pass metabolism effect. Seventy-two to 85% of the total drug is excreted as unchanged and the rest is metabolized to its five inactive metabolites in the liver. These metabolites are 4-trans-hydroxy-cyclohexyl form, 3-cis-hydroxy-cyclohexyl form, N-(2-acetylamino-ethyl-phenyl-sulphonyl)N'-cyclohexyl urea (DCDA) form and two unidentified metabolites. Sixty-five to 68% of the total amount of Glipizide (5% unchanged) is excreted in the urine in 24 h. As a result, Glipizide is either hydroxylated or transformed into its conjugated forms in the liver and rapidly excreted by the kidneys.

Formulation Types

The conventional tablet dosage forms and osmotic tablets of Glipizide exist as commercially available forms. The release of Glipizide from osmotic tablets, cyclodextrin complex osmotic tablets and controlled release tablets prepared with HPMC fits zero order kinetics. In addition, bilayered tablets prepared with HPMC, elementary osmotic tablets, lipospheres and mucoadhesive tablets are among other available dosage forms.

Conclusion

Glipizide is still the most common drug used in the treatment of NIDDM. Rapid absorption from the gastrointestinal channel, high antidiabetic potential, and variability in the antidiabetic mechanisms make Glipizide a favorite drug from the treatment perspective. The most important property of Glipizide is the decrease in absorption when it is taken with food. Furthermore, it does not exist in the breast milk and no serious side effect has been reported to date. As a result of this review, it can be concluded that with elevation in the duration time of Glipizide in the blood circulation, it will become a more forthcoming drug in the sulfonylurea class of drugs.

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