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RESEARCH ARTICLE

# Effects of *CYP2C9*3* and **13* alleles on the pharmacokinetics and pharmacodynamics of glipizide in healthy Korean subjects

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**Abstract** Glipizide is a second-generation sulfonylurea antidiabetic drug. It is principally metabolized to inactive metabolites by genetically polymorphic CYP2C9 enzyme. In this study, we investigated the effects of *CYP2C9*3* and **13* variant alleles on the pharmacokinetics and pharmacodynamics of glipizide. Twenty-four healthy Korean volunteers (11 subjects with *CYP2C9*1/*1*, 8 subjects with *CYP2C9*1/*3*, and 5 subjects with *CYP2C9*1/*13*) were recruited for this study. They were administered a single oral dose of glipizide 5 mg. The plasma concentration of glipizide was quantified for pharmacokinetic analysis and plasma glucose and insulin concentrations were measured as pharmacodynamic parameters. The results represented that *CYP2C9*3* and **13* alleles significantly affected the pharmacokinetics of glipizide. In subjects with *CYP2C9*1/*3* and *CYP2C9*1/*13* genotypes, the mean $AUC_{0-\infty}$ were increased by 44.8% and 58.2%, respectively (both $P < 0.001$), compared to those of subjects with *CYP2C9*1/*1* genotype, while effects of glipizide on plasma glucose and insulin levels were not significantly different between *CYP2C9* genotype groups. In conclusion, individuals carrying the defective *CYP2C9*3* and *CYP2C9*13* alleles have markedly elevated plasma concentrations of glipizide compared with *CYP2C9*1/*1* wild-type.

**Keywords** Glipizide · CYP2C9 · Genetic polymorphism · Genotype · Pharmacokinetics · Pharmacodynamics

## Introduction

Glipizide is a hypoglycemic sulfonylurea used for the treatment of type 2 diabetes mellitus. It is completely absorbed from the gastrointestinal tract and eliminated by extensive metabolism in the liver (Wåhlin-Boll et al. 1982). CYP2C9 is a major cytochrome P450 (CYP) enzyme in hepatic metabolism of glipizide (Kidd et al 1999; Kirchheiner et al. 2005b). *CYP2C9* is genetically polymorphic, and approximately 71 *CYP2C9* allele variants and subvariants (*CYP2C9*1B* to *CYP2C9*71*) have been identified to date (https://www.pharmvar.org/gene/CYP2C9). Among these mutations, *CYP2C9*3* (rs1057910, c.1075A > C, p.Ile359Leu) and *CYP2C9*13* (rs72558187, c.269T > C, p.Leu90Pro) variants are common in the East Asian population (Bae et al. 2011b), and they showed impaired enzyme activity and affected the plasma exposures of various substrates for the CYP2C9 enzyme (Bae et al. 2011a, 2012; Choi et al. 2011, 2012; Lee et al. 2015; Kim et al. 2017).

Although sulfonylurea antidiabetics are substrates of the CYP2C9 enzyme, the effects of *CYP2C9* genetic polymorphisms on the pharmacokinetics (PK) of these drugs are different depending on the individual drug. In the case of glimepiride, it was reported that area under the plasma concentration–time curve (AUC) was significantly increased in *CYP2C9* poor metabolizers, but slightly but not significantly

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increased in *CYP2C9* intermediate metabolizers (Kirchheiner et al. 2005b; Suzuki et al. 2006).

In previous studies, rifampin, an inducer of several CYP enzymes, decreased the mean $AUC_{0-\infty}$ of glipizide by 22% (Niemi et al. 2001), and fluconazole, a well-known CYP2C9 inhibitor, increased the mean AUC of glipizide by 56.9% (Pfizer Inc. 2008). But posaconazole, an inhibitor of both CYP3A4 and P-glycoprotein (MDR1) (Wexler et al. 2004; Sansone-Parsons et al. 2007), did not interact with glipizide (Courtney et al. 2003). Taken together, CYP2C9 was suggested to be the major metabolic enzyme for glipizide.

Kidd et al. (1999) performed the PK and pharmacodynamic (PD) study of glipizide. During the study, one subject experienced severe hypoglycemia with significantly low drug clearance, which was reported to be only 18% of the normal clearance. He was later found to be carrying the *CYP2C9*3/*3* genotype.

Relationship between *CYP2C9* genotypes and glipizide PK and PD should be investigated further for a proper usage of the drug. In Asian population, the most frequent variant of *CYP2C9* is the *CYP2C9*3* allele (Bae et al. 2005; Kirchheiner and Brockmöller 2005a). In addition, *CYP2C9*13* was identified in Korean (Bae et al. 2005, 2011b) and Chinese population (Si et al. 2004). *CYP2C9*13* allele also showed decreased enzyme activity in vitro (Guo et al. 2005a) and in vivo (Guo et al. 2005b; Bae et al. 2011a, 2012; Choi et al. 2011, 2012; Kim et al. 2017). To the best of our knowledge, no previous studies have been published that evaluated the effect of the *CYP2C9*13* allele on PK or PD parameters of glipizide. Therefore, we investigated the influence of *CYP2C9*3* and *CYP2C9*13* alleles on the glipizide PK and PD in Korean subjects in this study.

## Methods

### Genotyping

A 10 mL of blood sample was obtained from each subject, and deoxyribonucleic acid (DNA) was isolated by use of an extraction kit (Wizard Genomic DNA Purification Kit; Promega, Madison, WI, USA). The *CYP2C9*3* and *CYP2C9*13* polymorphisms were determined by a polymerase chain reaction-restriction fragment length polymorphism (PCR–RFLP) method as previously described (Bae et al. 2005).

### Subjects

Twenty-four healthy Korean volunteers (23 males and 1 female; 20–27 years, 60–80 kg) participated in the study (Table 1). Among the 24 subjects, 11 had *CYP2C9*1/*1* (wild-type), 8 had *CYP2C9*1/*3*, and 5 had *CYP2C9*1/*13* genotype. Written informed consent was obtained from each subject before participation in the study. All subjects were ascertained to be healthy by means of medical history, physical examination, electrocardiographic evaluation, and routine laboratory tests (blood chemical evaluation, hematologic test, and urine test) before they were enrolled in the study. They were instructed to avoid any medication and caffeine-containing beverages before and during the study.

**Table 1** Demographic data of subjects in different *CYP2C9* genotypes

| Genotype | Number of subjects | Age (years) | Weight (kg) | BMI (kg/m$^2$) |
|---|---|---|---|---|
| *CYP2C9*1/*1* | 11 | 23.1 ± 1.8 | 68.3 ± 4.8 | 22.3 ± 1.9 |
| *CYP2C9*1/*3* | 8 | 23.4 ± 0.7 | 68.6 ± 7.0 | 22.3 ± 1.9 |
| *CYP2C9*1/*13* | 5 | 23.6 ± 2.1 | 68.0 ± 4.7 | 22.7 ± 0.7 |

### Clinical study protocol

The study protocol was approved by the Institutional Review Board of the School of Pharmacy, Sungkyunkwan University, Suwon, Republic of Korea, and all procedures were performed in accordance with the recommendations of the Declaration of Helsinki on biomedical research involving human subjects.

After an overnight fast, each subject received a single oral dose of glipizide 5 mg (1 Digrin® 5 mg tablet, Yuhan Corporation, Seoul, Korea) with 240 mL of water. Glucose 75 g (1 bottle of Gluorange®, Lotte Pharm., Hwaseong, Korea) was administered 30 min after administration of glipizide. Meals were served 5 h and 9 h after administration of glipizide. Venous blood samples (7 mL each) were collected before and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 7, 9, 12, and 15 h after dosing. All blood samples were collected in lithium heparin tubes and centrifuged immediately. The separated plasma samples were stored at −70 °C until analysis.

### Pharmacokinetic analysis

Plasma glipizide concentrations were quantified by use of the HPLC method previously described (Wåhlin-Boll and Melander 1979) with modifications. In brief, to each 500 µL of plasma sample, 50 µL of internal standard solution (5 µg/mL tolbutamide), and 850 µL of 0.05 M HCl was added. After mixing, 5 mL of ethyl ether was added, and the tube was vortexed for 30 sec. Each sample was centrifuged at 2500 rpm for 10 min. The organic layer was transferred to a new tube and evaporated to dryness under a stream of nitrogen at 50 °C. The residue was reconstituted with 500 µL of 50% methanol, and 80 µL was injected for HPLC analysis.

The HPLC system consisted of Waters 515 HPLC pump, Waters 717 Plus Autosampler, and Waters 2487 Dual λ Absorbance Detector (Waters, Milford, MA, USA). The analytic column was a Bondclone C18 column (10 μm, 300 × 3.9 mm, Phenomenex, Torrance, CA, USA). A mixture of 0.01 M potassium phosphate monobasic and methanol (40:60 [vol/vol], pH 3.5) was used as the mobile phase, eluted at a flow rate of 1.0 mL/min. The elute was monitored at an ultraviolet wavelength of 225 nm.

The limit of quantification was 15 ng/mL for glipizide. The intra-day and inter-day coefficient of variation of the assay were 1.8% to 14.2% and 1.7% to 8.1%, respectively. The accuracy of the assay was 86.2% to 101.4%.

The PK of glipizide was characterized by peak concentration in plasma ($C_{max}$), concentration peak time ($t_{max}$), elimination half-life ($t_{1/2}$), and area under the plasma concentration–time curve from time 0 to 15 h ($AUC_{0-15}$) or to infinity ($AUC_{0-\infty}$). The $C_{max}$ and $t_{max}$ were taken directly from the original data. The elimination rate constant (ke) was calculated by the least-squares regression slope of the terminal plasma concentration. The $AUC_{0-\infty}$ was estimated as $AUC_{0-\infty} = AUC_{0-t} + C_t/ke$ (where $C_t$ is the last quantifiable drug concentration). The $t_{1/2}$ of glipizide was calculated as 0.693/ke. The apparent oral clearance (CL/F) of glipizide was calculated as $CL/F = Dose/AUC_{0-\infty}$.

### Pharmacodynamic analysis

Plasma glucose concentrations were measured by the glucose oxidase method with V-Glucose® (Asan Pharmaceutical, Seoul, Korea). Plasma insulin concentrations were determined by the radioimmunoassay with BioSource INS-IRMA Kit® (BioSource Europe S.A., Belgium).

The maximum increase and maximum decrease in plasma glucose concentrations from baseline plasma glucose values were calculated for the time period of 0 to 5 h, and the decremental area (net area below baseline) of plasma glucose from time 0 to 5 h (decremental glucose area 0–5 h) was determined by the linear trapezoidal rule.

The maximum increase in plasma insulin concentrations from baseline plasma insulin values was calculated for the time period of 0 to 5 h, and the incremental area (net area above baseline) of plasma insulin from time 0 to 5 h (incremental insulin area 0–5 h) was determined by the linear trapezoidal rule.

### Statistical analysis

The results are expressed as mean values ± standard deviation (SD). The PK parameters of glipizide and the insulin and glucose response to glipizide among three different groups were compared by use of one-way ANOVA, followed by Bonferroni t-test. For data without homogeneity of variance, Kruskal–Wallis ANOVA on Ranks test were performed and subsequently Dunn's test was conducted for multiple comparison. All data were analyzed with SigmaPlot 12® (Systat Software Inc., San Jose, CA, USA). Differences were considered to be statistically significant when $P$ value was $< 0.05$.

## Results

No clinically undesirable signs and symptoms possibly attributed to the administration of glipizide were observed throughout the study period. Table 1 summarizes the demographic and genotypic characteristics of the 24 normal healthy volunteers enrolled in this study. There was no significant difference in demographic characteristics among the genotype groups.

### Effects on pharmacokinetics of glipizide

The plasma concentration profiles, and PK parameters of glipizide are shown in Fig. 1 and Table 2. *CYP2C9* genotypes significantly affected the PK of glipizide (Table 2). The $AUC_{0-\infty}$ was significantly increased in subjects with variant *CYP2C9* allele ($P < 0.001$). *CYP2C9*1/*3* and *CYP2C9*1/*13* groups showed 36.4% ($P < 0.01$) and 57.0% ($P < 0.001$) decrease in $AUC_{0-\infty}$ compared to *CYP2C9*1/*1* group (wild-type). Similarly, *CYP2C9*1/*3* and *CYP2C9*1/*13* groups showed 42.4% ($P < 0.01$) and 52.4% ($P < 0.001$) decrease in $AUC_{0-15}$ compared to the wild-type genotype. The CL/F was also significantly decreased in subjects with *CYP2C9*1/*3* ($P < 0.01$) and *CYP2C9*1/*13* genotype ($P < 0.01$). *CYP2C9*1/*3* and *CYP2C9*1/*13* groups showed 34.8% and 40.7% decreased CL/F compared to *CYP2C9*1/*1* genotype.

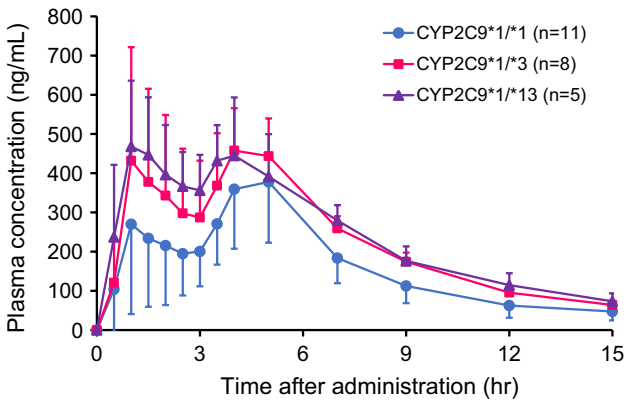


**Fig. 1** Plasma concentration–time profile of glipizide in different *CYP2C9* genotypes after a single 5 mg oral dose of glipizide. Circles, *CYP2C9*1/*1* (n = 11); squares, *CYP2C9*1/*3* (n = 8); triangles, *CYP2C9*1/*13* (n = 5). The data are given as arithmetic mean ± SD

**Table 2** Pharmacokinetic response of glipizide in healthy Korean subjects with different genotypes

| PK parameters | *CYP2C9*1/*1* n = 11 | *CYP2C9*1/*3* n = 8 | *CYP2C9*1/*13* n = 5 | *P* value |
|---|---|---|---|---|
| $C_{max}$ (ng/mL) | 511.4 ± 133.1 | 617.2 ± 100.3 | 572.7 ± 99.3 | N.S |
| $t_{max}$ (h) | 3.5 ± 1.5 | 2.8 ± 1.9 | 2.7 ± 1.6 | N.S |
| $t_{1/2}$ (h) | 3.4 ± 0.9 | 4.0 ± 1.0 | 4.6 ± 0.9 | N.S |
| CL/F (L/h) | 2.05 ± 0.55 | 1.34 ± 0.19** | 1.21 ± 0.14*** | < 0.001 |
| $AUC_{0\text{-}15}$ (ng·h/mL) | 2398.6 ± 629.4 | 3416.6 ± 408.9** | 3654.4 ± 385.8*** | < 0.001 |
| $AUC_{0-\infty}$ (ng·h/mL) | 2625.0 ± 782.3 | 3801.5 ± 504.7** | 4154.4 ± 464.2*** | < 0.001 |

$C_{max}$ maximum plasma concentration, $t_{max}$ time to reach peak plasma concentration, $t_{1/2}$ terminal elimination half-life, *CL/F* apparent oral clearance, *AUC* area under the plasma-time curve, *N.S.* not significant

**$P < 0.01$, versus *CYP2C9*1/*1*

***$P < 0.001$, versus *CYP2C9*1/*1*

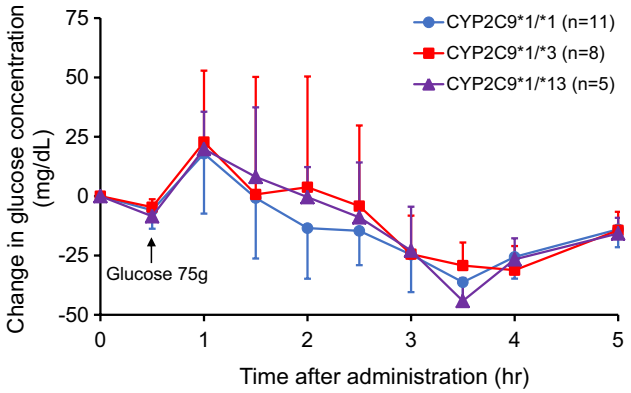


**Fig. 2** Changes in plasma glucose concentration in different *CYP2C9* genotypes after a single 5 mg oral dose of glipizide. Circles, *CYP2C9*1/*1* (n = 11); squares, *CYP2C9*1/*3* (n = 8); triangles, *CYP2C9*1/*13* (n = 5). The data are given as arithmetic mean ± SD

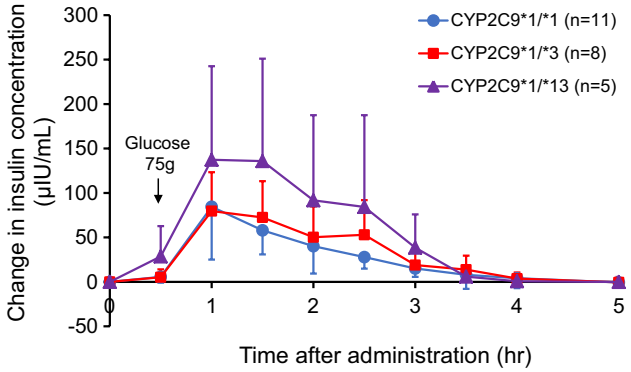


**Fig. 3** Changes in plasma insulin concentration in different *CYP2C9* genotypes after a single 5 mg oral dose of glipizide. Circles, *CYP2C9*1/*1* (n = 11); squares, *CYP2C9*1/*3* (n = 8); triangles, *CYP2C9*1/*13* (n = 5). The data are given as arithmetic mean ± SD

Other PK parameters, such as $C_{max}$, $t_{max}$, and $t_{1/2}$, were not significantly affected by *CYP2C9* genotypes.

### Effects on pharmacodynamics of glipizide

The PD responses and parameters of glipizide are shown in Figs. 2 and 3 and Table 3. Most PD parameters were not affected by the *CYP2C9* genetic polymorphisms (Table 3). Only maximum decrease in glucose concentration was significantly different among *CYP2C9* genotypes ($P < 0.05$). *CYP2C9*1/*13* group showed larger amount of decrease in glucose concentration. There was significant difference between *CYP2C9*1/*3* and *CYP2C9*1/*13*. However, significant differences were not found in the decremental area 0–5 h of glucose concentration between the subjects with different genotypes. Plasma insulin concentration also showed insignificant differences according to *CYP2C9* genotypes (Fig. 3 and Table 3).

## Discussion

The dose and frequency of a drug to obtain an appropriate therapeutic drug plasma concentration vary greatly depending on the patient. This is due to individual differences in drug absorption, distribution, metabolism and excretion, and these differences are determined by genetic factors as well as nongenetic variables, such as age, sex, body weight, liver function, commensal gut microbiota, nutritional and environmental factors (Correia 2021), co-administered drugs (Lee et al. 2019; Jung et al. 2020b), etc. Most drug metabolizing enzymes and transporters are genetically polymorphic, and these genetic polymorphisms influence PK and PD of drugs to varying degrees (Bae et al. 2011a, b, 2020; Lee et al. 2015, 2018; Kim et al. 2017, 2018a; Byeon et al. 2018, 2019; Jung et al. 2020a; Shin et al. 2020). Therefore, it is possible to minimize the difference in drug response in each individual by applying individual treatment strategies to each patient through the PBPK model that reflects the characteristics of both individual genetic factors and nongenetic

**Table 3** Pharmacodynamic response of glipizide in healthy Korean subjects with different genotypes

| PD parameters | *CYP2C9*1/*1* n = 11 | *CYP2C9*1/*3* n = 8 | *CYP2C9*1/*13* n = 5 | *P* value |
|---|---|---|---|---|
| Glucose response | | | | |
| Decremental glucose area 0–5 h (mg·h/dL) | 65.1 ± 43.2 | 48.5 ± 79.3 | 56.3 ± 34.4 | N.S |
| Maximum increase (mg/dL) | 21.4 ± 24.9 | 31.0 ± 38.8 | 27.9 ± 17.0 | N.S |
| Maximum decrease (mg/dL) | 42.4 ± 5.3 | 39.3 ± 5.3 | 48.9 ± 4.4[#] | 0.013 |
| Insulin response | | | | |
| Incremental insulin area 0–5 h (μIU·h/mL) | 122.2 ± 67.8 | 149.0 ± 72.7 | 261.4 ± 221.9 | N.S |
| Maximum increase (μIU/mL) | 90.4 ± 56.6 | 95.0 ± 37.0 | 158.5 ± 125.3 | N.S |

Glucose decremental area 0–5 h values and maximum decrease values are shown as positive values

*N.S.* not significant

[#]$P < 0.05$, versus *CYP2C9*1/*3*

variables (Duan et al., 2017; Kim et al. 2018b, 2021; Cho et al. 2021a, b; Jung et al. 2021). This is one way to realize personalized drug therapy or precision drug therapy.

In this study, glipizide plasma concentration was significantly increased in subjects with *CYP2C9* variant alleles. As oral bioavailability of glipizide is nearly 100% (Wensing 1989), increased plasma concentration of glipizide is due to decreased clearance rather than increased absorption. In *CYP2C9*1/*3* and *CYP2C9*1/*13* genotypes, CL/F was decreased by 34.8% and 40.7% compared to *CYP2C9*1/*1* genotype. Consequently, AUC of glipizide was increased in *CYP2C9*1/*3* and *CYP2C9*1/*13* genotypes compared to *CYP2C9*1/*1* genotype. The results of this study are consistent with those reported previously (Kidd et al. 1999; Tan et al. 2010). Similar patterns were observed in in vitro (Yang et al. 2018) as well as in vivo results. According to a report by Yang et al. (2018), the use of the recombinant enzyme system of CYP2C9 resulted in glipizide $CL_{int}$ reduction to 23% in CYP2C9*3 compared to CYP2C9*1. Although not included in this study, subjects with two reduced functional alleles of *CYP2C9* (*CYP2C9*3/*3*, *CYP2C9*3/*13* or *CYP2C9*13/*13*) would have shown a greater change in glipizide plasma concentrations. In addition, it was reported that glipizide is transported by OATP1B3 in vitro (Yang et al. 2018). *OATP1B3* is also affected by genetic polymorphisms. In order to more accurately evaluate the effect of genetic polymorphism on the in vivo PK of glipizide, genetic polymorphisms of *OATP1B3* should also be investigated.

In the present study, the mean CL/F value of glipizide in the *CYP2C9*1/*13* subjects were decreased by 40.7% compared with that in the *CYP2C9*1/*1* subjects. Likewise, the CL/F of celecoxib, irbesartan, lornoxicam, losartan, and meloxicam were previously shown to be decreased by 38.0% (Kim et al. 2017), 44.0% (Choi et al. 2012), 52.9% (Choi et al. 2011), 40.3% (Bae et al. 2012) and 62.1% (Bae et al. 2011a), respectively in individuals with the *CYP2C9*1/*13* genotype compared with those with the *CYP2C9*1/*1* genotype. Because the influence of *CYP2C9* polymorphism varies depending on the substrate, further evaluation of additional CYP2C9 substrates with narrow therapeutic ranges, such as warfarin and phenytoin, are required.

Dual peak plasma levels of glipizide were observed at glipizide concentration–time curves (Fig. 1). Some PK data related to this phenomenon have been reported (Wåhlin-Boll et al. 1982; Kidd et al. 1999; Jönsson et al. 2000; Tan et al. 2010). It may be due to enterohepatic circulation (Melander 1987), irregular absorption (Wåhlin-Boll et al. 1982; Jönsson et al. 2000), or simply a formulation problem. Concerning individual absorption patterns (data not shown), irregular absorption is probably the leading cause of the dual peak phenomenon.

In contrast to the PK effects, PD response was not significantly affected by *CYP2C9* genotypes. Only maximum decrease in glucose concentration was significantly low in *CYP2C9*1/*13* genotype compared with *CYP2C9*1/*3* genotype. It is assumed that healthy subjects can regulate glucose concentration well, so they would be affected less by hypoglycemic agents than the diabetic patients. Moreover, orally administered glucose could have partly obscured the hypoglycemic effect of glipizide. It has been reported that glipizide has a significant effect on the PD response. Tan et al. (2010) reported that *CYP2C9*3* allele carriers had significantly higher incremental insulin area 0–1 h after dosing in Chinese healthy subjects who received a single oral dose of glipizide 5 mg. In their study, oral glucose was dosed 1 h after glipizide administration, compared with 0.5 h in the present study. This difference in study design may result in difficulties when comparing the fasting-state insulin response after glipizide administration. Additionally, the irregular absorption of glipizide during the initial phase of 0–5 h post-dose made it difficult to evaluate the correlation between glipizide exposure and glucose/insulin response during the oral glucose tolerance test period. Chen et al. (2020) reported that *CYP2C9* carriers with two

reduced function alleles (*CYP2C9*2/*2*, *CYP*2/*3*, or *CYP*3/*3*) had a significantly higher incremental insulin area 0–4 h after dosing in the SUGAR-MGH study in subjects who received a single oral dose of glipizide 5 mg. In all three studies, including ours, plasma glucose responses to glipizide were not significantly affected by the *CYP2C9* genotype.

There are some controversial consequences regarding PD response of second-generation sulfonylurea among different *CYP2C9* genotype groups. In healthy subjects, glucose or insulin response was affected by the *CYP2C9* polymorphism (Kirchheiner et al. 2002; Yin et al. 2005; Suzuki et al. 2006) while other studies report no relation between PD and *CYP2C9* genotypes (Niemi et al. 2002). Niemi et al. (2002) reported that blood glucose responses to glyburide and glimepiride were not significantly affected by the *CYP2C9* genotype (*CYP2C9*2* or *CYP2C9*3* alleles). However, Yin et al. (2005) reported that a significantly higher rate of hypoglycemia (50% versus 17%), as well as a greater reduction in blood glucose concentration (at 2 h) after glyburide administration, occurred in the *CYP2C9*1/*3* subjects. Kirchheiner et al. (2002) reported that insulin secretion measured within 12 h after glyburide ingestion was higher in *CYP2C9*3/*3* group, whereas the differences in glucose concentrations were not significant. Suzuki et al. (2006) reported that the reduction of the HbA1c was larger in *CYP2C9*1/*3* group compared to *CYP2C9*1/*1* group in type 2 diabetes patients taking glimepiride. However, Klen et al. (2014) showed no significant differences in HbA1c reduction among the different genotypes of *CYP2C9* in a study conducted on Caucasian diabetic patients taking sulfonylurea.

The most important adverse drug reaction of sulfonylurea agents is hypoglycemia. As mentioned above, one subject with *CYP2C9*3/*3* genotype showed extremely low glucose concentration and had hypoglycemic symptoms such as feeling weak, having a rapid heart rate, sweating, and becoming pale after oral administration of glipizide 10 mg (Kidd et al. 1999). In one study (Holstein et al. 2004), they genotyped patients who experienced severe hypoglycemia while being treated with sulfonylurea agents (glimepiride and glyburide). They found that individuals with genetically determined low CYP2C9 activity were at an increased risk of sulfonylurea-associated severe hypoglycemia.

In conclusion, individuals carrying the defective *CYP2C9*3* and *CYP2C9*13* alleles had markedly elevated plasma concentration of glipizide, as compared with individuals homozygous for the *CYP2C9*1* allele. However, plasma glucose and insulin response to glipizide were not significantly affected by the *CYP2C9* genotypes in healthy subjects. We confirm that plasma concentration of glipizide is affected by *CYP2C9* genetic polymorphisms, especially in *CYP2C9*1/*13* and *CYP2C9*1/*13* genotype groups. But their effects on clinical use are still restrictive. Further well-controlled studies are required with long-term dosing of glipizide on diabetic patients with different *CYP2C9* genotypes.

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**Declarations**

**Conflict of interest** The authors declare that they have no conflict of interest.

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