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Effects of proton pump inhibitors on metformin pharmacokinetics and pharmacodynamics

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Effects of PPI on metformin PK and PD

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The number of text pages: 10

The number of tables: 3

The number of figures: 4

The number of references: 29

The number of words in the Abstract: 202

The number of words of Introduction: 450

The number of words of Discussion: 1157

Abbreviations

AUC, area under the concentration-time curve; AUG, area under the serum glucose concentration-time curve; BCS, Biopharmaceutics Classification System; CI, confidence interval; CL Cr, creatinine clearance; CL R, renal clearance; C max, the maximum concentration; CTC, Clinical Trials Center; DM, diabetes mellitus; GERD,
gastro-esophageal reflux disease; \( G_{\text{max}} \), the maximum serum glucose concentration; IC\(_{50}\), half-maximal inhibitory concentration; \( k_e \), elimination rate constant; LC/ESI-MS/MS, liquid chromatography electrospray ionization tandem mass spectrometry; MATE, multidrug and toxin extrusion protein; OCT, organic cation transporter; OGTT, oral glucose tolerance test; PD, pharmacodynamics; PK, pharmacokinetics; PMAT, plasma membrane monoamine transporter; PPIs, proton pump inhibitors; RMANOVA, repeated measures analysis of variance; SD, standard deviation; SrCL\(_R\), tubular secretion; \( T_{\text{max}} \), time to maximum plasma concentration
Abstract

As inhibitors of organic cation transporters (OCTs), proton pump inhibitors (PPIs) may affect the plasma levels of metformin, an OCT substrate. We investigated the effects of two PPIs, pantoprazole and rabeprazole, on metformin pharmacokinetics and glucose levels in healthy subjects. In this open, randomized, 6 × 3 cross-over study, 24 participants were administered metformin, either alone or in combination with pantoprazole or rabeprazole. The plasma concentrations of metformin and serum concentrations of glucose after a 75 g oral glucose tolerance test (OGTT) were determined. The area under the concentration-time curve (AUC) for metformin was 15% and 16% greater following co-administration with pantoprazole and rabeprazole, respectively. The maximum plasma metformin concentrations (C_max) also increased by 15% and 22%, respectively, compared to when it was administered without the PPIs. The percentage change in the AUC for glucose concentration versus time for metformin plus rabeprazole was significantly lower than that for metformin plus pantoprazole (geometric mean ratio: 0.96 [90% CI: 0.92–0.99] and 0.77 [0.63–0.93], respectively). There was no significant difference in the maximum glucose concentration. In conclusion, concomitant administration of PPIs with metformin significantly increased plasma metformin exposure, but the effects on glucose disposition were minor and varied depending on the PPI administered.
Introduction

Metformin is an oral insulin-sensitizing agent of the biguanide class and is used to treat type 2 diabetes mellitus (DM), as a monotherapy or combination therapy component. It works primarily by lowering hepatic glucose production and glucose absorption from the gastrointestinal tract and increasing insulin sensitivity and peripheral glucose uptake (Kirpichnikov et al., 2002). Metformin does not undergo hepatic metabolism and is excreted unchanged in urine. Its uptake in the liver is mediated by the organic cation transporter 1 (OCT1) (Higgins et al., 2012). Genetic variations in OCT1 are associated with differences in metformin pharmacokinetics (PK) (Shu et al., 2008). OCT2 is expressed in the kidney and contributes to metformin’s renal elimination (Song et al., 2008; Chen et al., 2009).

Gastrointestinal problems such as gastro-esophageal reflux disease (GERD) are common in type 2 DM patients (Sellin and Chang, 2008). GERD incidence tends to increase with an increase in the duration of diabetes, and is more common among patients using oral hypoglycemic agents (e.g., biguanides) than among those treated using dietary measures alone, or insulin therapy combined with other treatment modalities (Nishida et al., 2004). Although a proton pump inhibitor (PPI) is the treatment of choice for GERD, the overall prevalence of PPI treatment failure, defined as treatment with a PPI more than once daily, is significantly higher in diabetics than in non-diabetics (Hershcovici et al., 2012). However, there is no reported association between the type of diabetes medication and PPI treatment failure (Hershcovici et al., 2012).

Nies et al. demonstrated that PPIs can inhibit OCT1, OCT2, and OCT3 in vitro at half-maximal inhibitory concentrations (IC₅₀) ranging from 3 to 36 µM. The IC₅₀ values for the PPIs pantoprazole and rabeprazole against OCT2 and OCT1, respectively, were similar to the maximum plasma concentrations in humans (Nies et al., 2011). Moreover, PPIs affect the gastrointestinal absorption of many drug classes by altering the stomach pH (Budha et al., 2012). Fig. 1 depicts the various drug transporters involved in metformin disposition (Gong et al., 2012) and indicates the potential interactions between metformin and PPIs. These findings suggested that metformin co-administration with PPIs may cause undesired drug-drug interactions.

Self-reported poor glycemic control is independently associated with reflux symptoms; thus, metformin co-administration with a PPI is often necessary to control blood glucose levels and treat GERD (Bytzer et al., 2001; Bytzer et al., 2002). Although the results of Nies et al. (Nies et al., 2011) suggested that the plasma concentrations of PPIs achieved by routine dosing may be sufficient to inhibit OCT-mediated metformin
transport in vivo, whether such an interaction occurs in humans remains unknown. We aimed to test whether metformin’s PK or pharmacodynamics (PD) altered upon co-administration with pantoprazole or rabeprazole in healthy volunteers.
Materials and Methods

Subjects

The study protocol was approved by the Institutional Review Board of Seoul National University Bundang Hospital, Seongnam, Korea (B-1206/157-002). All procedures were conducted at the Clinical Trials Center (CTC) at Seoul National University Bundang Hospital, and were in accordance with the guidelines of the International Conference on the Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use–Korea Good Clinical Practice. Twenty-four healthy Korean males were enrolled in the study, and they provided informed written consent prior to enrolment. The baseline characteristics of the subjects were as follows: age, 25.9 ± 5.1 years; height, 173.1 ± 5.1 cm; and weight, 70.9 ± 8.5 kg. The exclusion criteria included abnormalities in clinical laboratory tests (hematology and chemistry), history of drug abuse, and medication use during the 14 days prior to investigational drug administration. Subjects were asked to limit alcohol consumption to < 30 g per day, to smoke < 10 cigarettes per day, and to consume 200–250 g of carbohydrates per day during the 7 days prior to drug administration. All but one subject completed the study. The results relating to the excluded subject were removed from the analyses because of the potential effect of alcohol consumption on metformin PK and PD.

Clinical study design

This was a 6-sequence, 3-period crossover study (6 × 3 Williams design) designed to compare the effects of metformin alone with those of metformin combined with pantoprazole or rabeprazole. Pantoprazole (40 mg, p.o.; Pantoloc Tab; PacificPharma, Seoul, Korea) or rabeprazole (20 mg, p.o.; Pariet Tab; Janssen Korea, Seoul, Korea) was administered on day -2. The next day (day -1), the participants were admitted to the CTC and fed a standard dinner. At 8 PM, the participants were given metformin (750 mg p.o.; Diabex Tab; Daewoong Pharmaceutical, Seoul, Korea) with or without PPIs according to their treatment assignment. The following day (day 1) at 8 AM, the subjects were given metformin 500 mg (p.o.) with or without PPIs after fasting for at least 10 h (Table 1). Two hours after drug administration, an oral glucose tolerance test (OGTT) was conducted following ingestion of a 75 g glucose load (Gluorange®; Korea Mcnulty’s Co. Ltd., Hwaseong, Korea). After one week’s washout-period, the same procedures were applied to the subjects as the treatment assignment.
Blood and urine collection

Blood samples were collected for measuring plasma metformin concentrations on day 1 of each admission period, before dosing and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 h after drug administration. Urine samples were collected for metformin analysis from 0 to 12 h after drug administration. To calculate creatinine clearance (CL\textsubscript{Cr}), serum creatinine levels were measured in blood samples obtained before dosing. Blood samples for determining glucose concentration during OGTTs were collected immediately before and 15, 30, 45, 60, 90, 120, 150, and 180 min after glucose ingestion.

Metformin concentration analysis

Metformin concentrations in plasma and urine were determined using liquid chromatography electrospray ionization tandem mass spectrometry (LC/ESI-MS/MS; Agilent 1260 series and Agilent 6460 Quadrupole, Agilent Technologies, Inc., Santa Clara, CA, USA). Simple protein precipitation was carried out by adding 450 μL of protein precipitation solvent (100% acetonitrile) containing an internal standard (phenformin) to 50 μL of plasma or urine. The mixture was vortexed for 10 min and centrifuged at 18,374 g for 10 min. An aliquot of the supernatant was transferred to a vial, and 1 μL of this sample solution was injected into the LC-MS system column (Kinetex HILIC, 50 × 2.1 mm, 5 μm, Phenomenex, Torrance, CA, USA). The isocratic mobile phase was composed of 5 mM ammonium formate in distilled water (pH 6.2) and 100% acetonitrile. The limits of quantification were 5.62 ng/mL in plasma and 0.1 μg/mL in urine; determination coefficients (R\textsuperscript{2}) were > 0.994 and > 0.995, respectively. The intra-day and inter-day coefficients of variation were both < 10%.

OGTT analysis

The total area under the serum glucose concentration-time curve (AUG) from 0 to 180 min after glucose ingestion was calculated using the linear trapezoidal rule. The maximum glucose concentration (G\text{max}) was determined from the measured values. The percentage change from baseline of these parameters were also calculated and referred to as %AUG and %G\text{max}, respectively.

PK and statistical analyses

PK parameters were calculated in a non-compartmental analysis using Phoenix 6.3 (Pharsight,
Mountain View, CA, USA). Metformin C\textsubscript{max} and time to reach C\textsubscript{max} (T\textsubscript{max}) were determined from measured values. The area under the metformin concentration-time curve (AUC) from 0 to 12 h after dosing was calculated using the linear trapezoidal rule. The elimination rate constant (k\textsubscript{e}) was estimated from the slope of the best-fit line determined by linear regression analysis of the log-transformed concentration-time curve. The elimination half-life (t\textsubscript{1/2}) was calculated using the following equation: t\textsubscript{1/2} = \ln(2)/k\textsubscript{e}. The renal clearance (CL\textsubscript{R}) of metformin was calculated as the total amount of metformin excreted in the urine over 12 h, divided by the AUC of metformin. The Cockcroft-Gault equation ([140 - age] × [body weight, kg]/[72 × serum creatinine]) was used to calculate CL\textsubscript{Cr}. Metformin’s renal clearance by tubular secretion (SrCL\textsubscript{R}) was calculated by subtracting CL\textsubscript{Cr} from the metformin CL\textsubscript{R}.

The arithmetic mean was calculated for each PK and OGTT parameter, and these were expressed as the mean ± standard deviation (SD). The geometric mean was also calculated for each PK and OGTT parameter. The ratio of the geometric means were determined among the treatment assignments as follows: metformin and pantoprazole co-administration to that of metformin alone, metformin and rabeprazole co-administration to that of metformin alone, and metformin and rabeprazole co-administration to that of metformin and pantoprazole co-administration (90% confidence interval [CI]). Repeated measures analysis of variance (RMANOVA) was used to evaluate differences in glucose levels associated with drug treatments. The statistical analyses were performed using SAS\textsuperscript{®} 9.3 software (SAS Institute Inc., Cary, NC, USA). Differences were considered statistically significant at \( p < 0.05 \).
Results

Metformin PK

The plasma concentration profiles of metformin alone and metformin co-administered with pantoprazole or rabeprazole are shown in Fig. 2. The metformin AUCs were increased by 15% and 16% when metformin was co-administered with pantoprazole and rabeprazole, respectively, than when it was administered alone (Tables 2 and 3). The metformin C\text{max} values also increased by 15% and 22% when metformin was co-administered with pantoprazole and rabeprazole, respectively (Tables 2 and 3). Pantoprazole and rabeprazole elicited comparable increases in the metformin AUC and C\text{max} values (Table 3). The T\text{max}, CL\text{R}, and SrCL\text{R} of metformin were not significantly altered by pantoprazole or rabeprazole co-administration (Table 3).

Effects of PPIs on the glucose-lowering effect of metformin

The serum glucose concentration-time curves for the OGTTs are shown in Fig. 3. There were no differences in the arithmetic means of the G\text{max}, %G\text{max}, AUG, or %AUG among the 3 treatment groups (Table 2). However, when viewed in terms of the geometric mean ratio, the AUG of metformin plus rabeprazole was significantly lower than that of metformin plus pantoprazole (geometric mean ratio: 0.96 [90% CI: 0.92–0.99]; Table 3). Similarly, the %AUG and the %G\text{max} were significantly lower with rabeprazole co-administration than with pantoprazole co-administration; the corresponding geometric mean ratios were 0.77 (90% CI: 0.63–0.93) and 0.89 (90% CI: 0.79–0.99) (Table 3).

RMANOVA revealed a significant between-subject treatment effect on the glucose profiles (p = 0.012). Time was a significant component of the within-subject effect (p < 0.001), but there was no period effect. The overall mean differences in serum glucose concentrations only differed significantly between rabeprazole and pantoprazole treatments (4.45 mg/dL [95% CI: 0.77–8.12]). The difference in serum glucose concentrations when metformin was administered alone and in combination with pantoprazole was 0.09 mg/dL (95% CI: -4.58–2.77), whereas that when metformin was administered in combination with rabeprazole was 3.55 mg/dL (95% CI: -0.13–7.22).

The PK-PD relationships for metformin were quantified by AUG-AUC and %AUG-AUC correlations, which are shown in Fig. 4. Non-parametric local regression showed a flat relationship up to an AUC of 10,000 ng/mL\cdot h. Linear regression analysis yielded an r^2 < 0.1 for both AUG and %AUG.
Discussion

We employed a 6 × 3 crossover Williams design to examine whether PPIs affected metformin PK or PD in healthy male volunteers. We showed that pantoprazole and rabeprazole each increased the plasma level of metformin, but they had no effect on metformin CL\textsubscript{R}. Although the PPIs increased the plasma metformin concentration, they had no other effect on the OGTT serum glucose profiles. We also found that the PK-PD relationship for metformin was flat up to an AUC of 10,000 ng/mL\cdot h, as we did not observe any slope in the regression line between AUC and AUG or %AUG. Therefore, the drug interaction effects on the glucose-lowering actions of metformin were not dependent on the plasma concentrations of metformin. This finding was consistent with the observation that fluctuations in plasma concentrations were not clinically significant (Schwartz et al., 2006), and that metformin had a long residence time in the liver and other effector compartments (Sambol et al., 1996).

Although the differences were not statistically significant, co-administration of pantoprazole or rabeprazole with metformin resulted in slightly higher and lower glucose profiles, respectively, than that of metformin alone. The comparative effects of rabeprazole and pantoprazole on metformin PD were significant, as indicated by the geometric mean ratios and RMANOVA results. The percentage change in glucose levels, as indicated by %AUG and %G\textsubscript{max}, was lower with rabeprazole co-administration than with pantoprazole co-administration. However, the magnitude of this difference was minimal and its statistical significance was dependent on how the data were analyzed. The overall mean difference of 4.45 mg/dL from the RMANOVA corresponds to less than 3% of the G\textsubscript{max}. Therefore, we conclude that the two PPIs had comparable effects on metformin PD.

The observed increase in plasma levels of metformin may have resulted from both the direct and indirect effects of PPIs on metformin absorption from the gastrointestinal tract. PPIs inhibit OCTs \textit{in vitro} (Nies et al., 2011), but OCT inhibition in the intestine would be expected to decrease absorption. In addition, the plasma membrane monoamine transporter (PMAT), which is expressed in the human intestine, is involved in metformin uptake, and is reportedly more active in acidic environments (Zhou et al., 2007). However, a more plausible explanation is that PPIs inhibit OCT1-mediated uptake of metformin in the liver. The estimated concentrations of PPIs in the portal vein are 2- to 4-fold higher than the C\textsubscript{max} observed in the systemic circulation. These portal vein levels approach the IC\textsubscript{50} values for OCT1 (Nies et al., 2011). Limiting the distribution of metformin to the
liver would be expected to increase its initial plasma concentration. Consideration of the ratio of the unbound concentration of an inhibitor to its IC₅₀ has been recommended for assessment of the potential for transporter-mediated drug interaction (International Transporter Consortium et al., 2010). However, protein binding of both PPIs used in this study was reported to be >95% (Stedman and Barclay, 2000). In the present study, the ratio values for OCT1 and OCT2 were <0.1, a value that was below the level considered necessary to justify further in vivo studies. Irrespective of the method selected to assess drug interactions (Ito et al., 2002), caution should be exercised when calculating this ratio for OCT1 inhibition because the maximal unbound portal vein concentration cannot be quantified precisely. The results of the present study, showing an initial increase in plasma metformin levels, indicated that the possibility of OCT1 inhibition could not be excluded. Multidrug and toxin extrusion protein (MATE) transporters and OCT2 are mainly involved in urinary excretion of metformin, and PPIs may also inhibit these transporters (Nies et al., 2011; Wittwer et al., 2013). However, the impact of OCT2 inhibition on the renal clearance of metformin is controversial (Ito et al., 2012). In this study, the extent of inhibition of OCT2 and MATE1 by PPIs was thought to be minimal because there were no differences in CLR or elimination half-life between the treatment groups.

PPIs may also increase metformin absorption indirectly by increasing gastric pH, thereby increasing the dissolution of metformin hydrochloride in a more alkaline environment. The pKa of metformin is 11.5, and the drug is predominantly ionized in the gastrointestinal tract. In vitro dissolution tests have shown that metformin hydrochloride tablets dissolve faster in pH 6.8 phosphate buffer than in 0.1 N HCl and pH 4.5 acetate buffer (Desai et al., 2014). In addition, under the Biopharmaceutics Classification System (BCS), metformin is classified as a class III drug, with high solubility and low permeability. Thus, a more alkaline environment may facilitate metformin absorption (Graham et al., 2011). Moreover, Padwal et al. reported that metformin AUC increased by 21% in patients who underwent gastric bypass (Padwal et al., 2011).

Clinical studies examining the effects of PPIs on glycemic control have yielded conflicting results (Boj-Carceller et al., 2011; Crouch et al., 2012; Hove et al., 2013). To our knowledge, no study has investigated the short-term effects of PPIs co-administered with metformin on glucose profiles in OGGTs. Our study showed that baseline glucose levels were comparable among treatments, and that PPIs had no additive effect on reduction of glucose levels, even though they increased metformin concentrations. These data suggested that PPIs had only a minor direct effect on glucose levels during OGGTs.
This study had some limitations. First, our findings could not be directly extrapolated to predict clinical responses to metformin, because the study was conducted over a short time-frame and with healthy volunteers. The metformin PK-PD relationship has been reported to be altered in patients with type 2 DM, compared with healthy subjects, although metformin PK were not affected in the disease (Sambol et al., 1996). A modest increase in systemic exposure and/or exposure at the site of action could lead to an alteration in the glucose-lowering effects of metformin in patients with type 2 DM, compared to healthy individuals. Further study is therefore necessary to extend our results to patients with DM. Second, the effect of PPI-mediated OCT inhibition may be concentration-dependent, but plasma PPI concentrations were not measured in this study. Therefore, their respective PK profiles may have varied significantly, depending on the CYP2C19 genotypes of the study participants (Yang et al., 2009; Gawronska-Szklarz et al., 2012). However, the plasma concentrations of PPIs may not reflect their concentration at the site of inhibition (the portal vein for OCT1) and in addition, we are confident that the crossover study design prevented this issue from biasing our results.

To our knowledge, this study is the first to examine whether PPIs affected the PK and PD of metformin in humans. We found that concomitant administration of metformin and PPIs increased plasma levels of metformin, but this had minor effect on the glucose-reducing actions of metformin. We therefore conclude that while transporter-mediated drug-drug interactions may alter drug PK, this does not necessarily translate into an effect on PD. It may be necessary to study these effects in patients with type 2 DM to determine whether PPIs affect the clinical efficacy and safety of metformin.
Acknowledgements

We thank the staff of the SNU Bundang Hospital Clinical Trials Center for their generous cooperation and Yu Mi Oh for her excellent technical assistance with drug concentration analysis.
Authorship Contributions

Participated in research design: I. Chung, J. Chung, Cho, and Yu.

Conducted experiments: I. Chung and Kim.

Contributed new reagents or analytic tools: Yoon,

Performed data analysis: Kim and J. Chung.

Wrote or contributed to the writing of the manuscript: Kim, J. Chung, Lim, Lee, and Jang.
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Nishida T, Tsuji S, Tsuji M, Arimitsu S, Sato T, Haruna Y, Miyamoto T, Kanda T, Kawano S, and Hori M


Footnotes

This work was supported by the Basic Science Research Program through the National Research Foundation of Korea [Grant NRF-2011-0009540]; and Seoul National University and Bundang Hospital Research Fund [Grant 06-2013-101].
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Figure Legends

Figure 1. The potential interactions and effects of proton pump inhibitors on metformin pharmacokinetics and pharmacodynamics. [Modified from PharmGKB. Copyright to PharmGKB and state that permission has been given by PharmGKB and Stanford University. An original version is available online at http://www.pharmgkb.org/pathway/PA165948259.]

Figure 2. Plasma concentration-time curves of metformin after treatment with metformin alone, and combined with pantoprazole or rabeprazole. Data are presented as mean ± SD.

Figure 3. Serum glucose concentration-time curves produced by the oral glucose tolerance test after treatment with metformin alone, and combined with pantoprazole or rabeprazole. Data are presented as mean ± SD.

Figure 4. Correlations between (A) the area under the metformin concentration-time curve (AUC) and area under the glucose concentration-time curve (AUG), and (B) AUC and %AUG. Middle lines represent local regression.
## Tables

**Table 1** Study drug administration schedule.

<table>
<thead>
<tr>
<th>Group (Number of subjects)</th>
<th>Period 1 (Day -2 – Day 1)</th>
<th>Period 2 (Day 6 – Day 8)</th>
<th>Period 3 (Day 13 – Day 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (4) Metformin</td>
<td>Metformin</td>
<td>Metformin +</td>
<td>Metformin +</td>
</tr>
<tr>
<td>2 (4) Metformin</td>
<td>Metformin</td>
<td>Metformin +</td>
<td>Metformin +</td>
</tr>
<tr>
<td>Cross-over</td>
<td>Rabeprazole</td>
<td>Metformin +</td>
<td>Rabeprazole</td>
</tr>
<tr>
<td>3 (4) Metformin +</td>
<td>Metformin</td>
<td>Metformin +</td>
<td>Metformin +</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>Rabeprazole</td>
<td>Metformin +</td>
<td>Rabeprazole</td>
</tr>
<tr>
<td>4 (4) Metformin +</td>
<td>Metformin +</td>
<td>Metformin +</td>
<td>Metformin</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>Rabeprazole</td>
<td>Metformin +</td>
<td></td>
</tr>
<tr>
<td>5 (4) Metformin +</td>
<td>Metformin +</td>
<td>Metformin +</td>
<td>Metformin</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>Pantoprazole</td>
<td>Metformin +</td>
<td></td>
</tr>
<tr>
<td>6 (4) Metformin +</td>
<td>Metformin</td>
<td>Metformin +</td>
<td></td>
</tr>
<tr>
<td>Rabeprazole</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Metformin: 750 mg at 8 PM on day-1 and 500 mg at 8 AM on day 1 in all periods.

Pantoprazole 40 mg or rabeprazole 20 mg were administered at 4–6 PM on day -2, 8 PM on day -1, and 8 AM on day 1 in each scheduled period.
Table 2  Pharmacokinetic parameters and oral glucose tolerance test results after administration of metformin alone, metformin plus pantoprazole, or metformin plus rabeprazole in healthy subjects (n = 23).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Metformin</th>
<th>Metformin + Pantoprazole</th>
<th>Metformin + Rabeprazole</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (ng/mL·h)</td>
<td>5863 ± 1531</td>
<td>6758 ± 2034</td>
<td>6770 ± 1710</td>
<td>0.145</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>1112 ± 267</td>
<td>1287 ± 360</td>
<td>1342 ± 271</td>
<td>0.032</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.5 (1.0, 2.5)</td>
<td>1.5 (0.5, 2.5)</td>
<td>2 (0.5, 2.5)</td>
<td>0.902</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>3.53 ± 0.60</td>
<td>3.38 ± 0.69</td>
<td>3.28 ± 0.54</td>
<td>0.376</td>
</tr>
<tr>
<td>fe</td>
<td>0.66 ± 0.26</td>
<td>0.70 ± 0.23</td>
<td>0.75 ± 0.32</td>
<td>0.512</td>
</tr>
<tr>
<td>CLR (mL/min)</td>
<td>967 ± 316</td>
<td>889 ± 238</td>
<td>916 ± 278</td>
<td>0.631</td>
</tr>
<tr>
<td>CLcr (mL/min)</td>
<td>131 ± 26</td>
<td>129 ± 24</td>
<td>129 ± 23</td>
<td>0.975</td>
</tr>
<tr>
<td>SrCLr (mL/min)</td>
<td>837 ± 312</td>
<td>761 ± 239</td>
<td>788 ± 276</td>
<td>0.636</td>
</tr>
<tr>
<td>Glucose0h</td>
<td>84.7 ± 5.9</td>
<td>85.4 ± 5.8</td>
<td>85.7 ± 6.0</td>
<td>0.845</td>
</tr>
<tr>
<td>AUG (mg/dL·min)</td>
<td>20,939 ± 2934</td>
<td>21,067 ± 2256</td>
<td>20,188 ± 2,326</td>
<td>0.448</td>
</tr>
<tr>
<td>Gmax (mg/dL)</td>
<td>143 ± 18</td>
<td>144 ± 16</td>
<td>139 ± 16</td>
<td>0.618</td>
</tr>
<tr>
<td>Tglc_max (min)</td>
<td>60 (30, 150)</td>
<td>45 (30, 150)</td>
<td>45 (30, 150)</td>
<td>0.284</td>
</tr>
<tr>
<td>%AUG (%·min)</td>
<td>6,735 ± 3,189</td>
<td>6,739 ± 2,153</td>
<td>5,709 ± 2,485</td>
<td>0.320</td>
</tr>
<tr>
<td>%Gmax (%)</td>
<td>68.7 ± 20.3</td>
<td>68.7 ± 13.6</td>
<td>62.9 ± 18.7</td>
<td>0.440</td>
</tr>
</tbody>
</table>

The data shown for each parameter are mean ± SD, with the exception of Tmax and Gmax data, presented as the median, minimum, and maximum. AUC, area under the plasma concentration-time curve from time point 0 h to the final time-point at 12 h; Cmax, maximum plasma concentration; Tmax, time to maximum plasma concentration; t1/2, elimination half-life; fe, fraction excretion unchanged; CLR, renal clearance; CLcr, creatinine clearance; SrCLR, renal clearance by tubular secretion; Glucose0h, serum glucose concentration before oral glucose tolerance test; AUG, total area under the serum concentration-time curve for glucose (0–180 min after ingestion); Gmax, maximum serum glucose concentration; Tglc_max, time of maximum serum glucose concentration; %AUG, total area under the
change (%) of glucose level-time curve; %G_{\text{max}}$, maximum change (%) in glucose concentration
Table 3 Geometric mean ratios of pharmacokinetic and glucose parameters among three treatments in healthy participants ($n = 23$).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GMR of P to M (90% CI)</th>
<th>GMR of R to M (90% CI)</th>
<th>GMR of R to P (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (ng/mL·h)</td>
<td>1.15 (1.06–1.24)*</td>
<td>1.16 (1.07–1.26)*</td>
<td>1.01 (0.93–1.10)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>1.15 (1.06–1.26)*</td>
<td>1.22 (1.12–1.33)*</td>
<td>1.06 (0.97–1.15)</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$f_e$</td>
<td>1.09 (0.93–1.27)</td>
<td>1.12 (0.95–1.31)</td>
<td>1.03 (0.88–1.21)</td>
</tr>
<tr>
<td>$\text{CL}_R$ (mL/min)</td>
<td>0.95 (0.83–1.08)</td>
<td>0.97 (0.84–1.11)</td>
<td>1.02 (0.89–1.17)</td>
</tr>
<tr>
<td>$\text{SrCL}_R$ (mL/min)</td>
<td>0.98 (0.80–1.20)</td>
<td>1.00 (0.81–1.23)</td>
<td>1.02 (0.83–1.25)</td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUG (mg/dL·min)</td>
<td>1.01 (0.97–1.05)</td>
<td>0.97 (0.93–1.00)</td>
<td>0.96 (0.92–0.99)*</td>
</tr>
<tr>
<td>$%\text{AUG}$ (%·min)</td>
<td>1.08 (0.89–1.32)</td>
<td>0.83 (0.69–1.01)</td>
<td>0.77 (0.63–0.93)*</td>
</tr>
<tr>
<td>$G_{\text{max}}$ (mg/dL)</td>
<td>1.01 (0.97–1.05)</td>
<td>0.98 (0.94–1.02)</td>
<td>0.97 (0.93–1.01)</td>
</tr>
<tr>
<td>$%G_{\text{max}}$ (%)</td>
<td>1.03 (0.92–1.16)</td>
<td>0.92 (0.82–1.02)</td>
<td>0.89 (0.79–0.99)*</td>
</tr>
</tbody>
</table>

* $p < 0.05$; M = metformin alone; P = metformin + pantoprazole; R = metformin + rabeprazole; GMR = geometric mean ratio; CI = confidence interval.

AUC, area under the plasma concentration-time curve from time-point 0 h to time-point 12 h; $C_{\text{max}}$, maximum plasma concentration; $f_e$, fraction excretion unchanged; $\text{CL}_R$, renal clearance; $\text{SrCL}_R$, renal clearance by tubular secretion; AUG, total area under the serum concentration-time curve for glucose (0–180 min after ingestion); $G_{\text{max}}$, maximum serum glucose concentration; $\%\text{AUG}$, total area under the change (%) of glucose level-time curve; $\%G_{\text{max}}$, maximum change (%) in glucose concentration.