Effects of Proton Pump Inhibitors on Metformin Pharmacokinetics and Pharmacodynamics

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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, six-sequence, three-period crossover 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 coadministration with pantoprazole and rabeprazole, respectively. The maximum plasma metformin concentrations (Cmax) also increased by 15% and 22%, respectively, compared with 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% confidence interval: 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 gastroesophageal 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 patients with diabetes than in nonpatients with diabetes (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., (2011) 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. Moreover, PPIs affect the gastrointestinal absorption of many drug classes by altering the stomach pH (Budha et al., 2012). Figure 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 coadministration with PPIs may cause undesired drug-drug interactions.

Self-reported poor glycemic control is independently associated with reflux symptoms; thus, metformin coadministration with a PPI is often necessary to control blood glucose levels and treat GERD (Bytzer et al., 2001, 2002). Although the results of Nies et al. (2011) suggested that the plasma concentrations of PPIs achieved by routine

ABBREVIATIONS: AUC, area under the concentration-time curve; AUG, area under the serum glucose concentration-time curve; CI, confidence interval; CLcr, creatinine clearance; CLr, renal clearance; Cmax, the maximum concentration; DM, diabetes mellitus; GERD, gastroesophageal reflux disease; Gmax, maximum serum glucose concentration; IC50, half-maximal inhibitory concentration; LC-MS, liquid chromatography–mass spectrometry; OCT, organic cation transporter; OGTT, oral glucose tolerance test; PD, pharmacodynamics; PK, pharmacokinetics; PPIs, proton pump inhibitors; RMANOVA, repeated-measures analysis of variance; SrClr, tubular secretion; Tmax, time to maximum plasma concentration.
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 coadministration 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 at Seoul National University Bundang Hospital and were in accordance with the guidelines of the International Conference on the Harmonization 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 enrollment. The baseline characteristics of subjects were: 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 six-sequence, three-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, by mouth; Pantoloc Tab; Pacificpharma, Seoul, Korea) or rabeprazole (20 mg, by mouth; Pariet Tab; Janssen Korea, Seoul, Korea) was administered on day –2. The next day (day –1), the participants were admitted to the Clinical Trials Center and fed a standard dinner. At 8 PM the participants were given metformin (750 mg by mouth; Diabex tablet; Daewoong Pharmaceutical Co., 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 (by mouth) with or without PPIs after fasting for at least 10 hours (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 hours after drug administration. Urine samples were collected for metformin analysis from 0 to 12 hours after drug administration. To calculate creatinine clearance (CLcr), 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 minutes 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). Simple protein precipitation was carried out by adding 450 µl of protein precipitation solvent (100% acetonitrile) containing an internal standard (phenformin; Sigma-Aldrich, Yongin, Korea) to 50 µl of plasma or urine. The mixture was vortexed for 10 minutes and centrifuged at 18,374g for 10 minutes. 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,
were used to evaluate differences in glucose levels associated with drug treatments. Repeated-measures analysis of variance (RMANOVA) was calculated by subtracting CLCr from the metformin CLR. Metformin clearance (CLR) of metformin was calculated as the total amount of metformin excreted in the urine over 12 hours, divided by the AUC of metformin. The Cockcroft-Gault equation ([140 – age] × [body weight, kg]/72 × serum creatinine]) was used to calculate CLCr. Metformin’s renal clearance by tubular secretion (SrCLR) was calculated by subtracting CLCr from the metformin CLR.

The arithmetic mean was calculated for each PK and OGTT parameter, and these were expressed as the mean ± S.D. 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 coadministration to that of metformin alone, and metformin and rabeprazole coadministration to that of metformin plus pantoprazole [geometric mean ratio: 0.96 (90% CI: 0.92–0.99); Table 3]. Similarly, the %AUG and the %Gmax were significantly lower with rabeprazole coadministration than with pantoprazole coadministration; 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 to 2.77), whereas the difference 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. Nonparametric local regression showed a flat relationship up to an AUC of 10,000 ng/ml * h. Linear regression analysis yielded an $r^2 < 0.1$ for both AUG and %AUG.

**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 $G_{\text{max}}$, %Gmax, AUG, or %AUG among the three 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 %Gmax were significantly lower with rabeprazole coadministration than with pantoprazole coadministration; 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).

**Results**

**Metformin PK.** The plasma concentration profiles of metformin alone and metformin coadministered with pantoprazole or rabeprazole are shown in Fig. 2. The metformin AUCs were increased by 15% and 16% when metformin was coadministered with pantoprazole and rabeprazole, respectively, than when it was administered alone (Tables 2 and 3). The metformin Cmax values also increased by 15% and 22% when metformin was coadministered with pantoprazole and rabeprazole, respectively (Tables 2 and 3). Pantoprazole and rabeprazole elicited comparable increases in the metformin AUC and Cmax values (Table 3). The Tmax, CLR, and SrCLR of metformin were not significantly altered by pantoprazole or rabeprazole coadministration (Table 3).
Effects of PPIs on Metformin PK and PD

Tables 2 and 3

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>CLg (ml/min)</td>
<td>967 ± 316</td>
<td>889 ± 238</td>
<td>916 ± 278</td>
<td>0.631</td>
</tr>
<tr>
<td>CLh (ml/min)</td>
<td>131 ± 26</td>
<td>129 ± 24</td>
<td>129 ± 23</td>
<td>0.975</td>
</tr>
<tr>
<td>SrCLg (ml/min)</td>
<td>837 ± 312</td>
<td>761 ± 239</td>
<td>788 ± 276</td>
<td>0.636</td>
</tr>
<tr>
<td>Glucose0h (mg/dl)</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>Tgmax (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>

C, fraction excretion unchanged; 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); Tgmax, time of maximum serum glucose concentration; %AUG, total area under the change (% of glucose level–time curve; %Gmax, 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>Metformin</th>
<th>Metformin + Pantoprazole</th>
<th>Metformin + Rabeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetics 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>Cmax (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>t1/2 (h)</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>CLg (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>SrCLg (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 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>%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>Gmax (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>%Gmax (%)</td>
<td>1.03 (0.92–1.16)</td>
<td>0.92 (0.82–1.02)</td>
<td>0.93 (0.79–0.99)*</td>
</tr>
</tbody>
</table>

AUG, total area under the serum concentration-time curve for glucose (0–180 min after ingestion); %AUG, total area under the change (% of glucose level–time curve; %Gmax, maximum change (%) in glucose concentration; GMR, geometric mean ratio.

*P < 0.05

Discussion

We employed a crossover 6 × 3 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 CLg. 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 · hour, 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 statistically 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 %Gmax, was lower with rabeprazole coadministration than with pantoprazole coadministration. 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 Gmax. 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 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 Cmax observed in the systemic circulation. These portal vein levels approach the IC50 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 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. (2011) reported that metformin AUC increased by 21% in patients who underwent gastric bypass.

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 coadministered with metformin on glucose profiles in OGTTs. 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 OGTTs.

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 with 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 the results.

To our knowledge, this study is the first to examine whether PPIs affect 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.

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Authorship Contributions


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