—Review—

Clinical Usefulness of Limited Sampling Strategies for Estimating AUC of Proton Pump Inhibitors

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Cytochrome P450 (CYP) 2C19 (CYP2C19) genotype is regarded as a useful tool to predict area under the blood concentration-time curve (AUC) of proton pump inhibitors (PPIs). In our results, however, CYP2C19 genotypes had no influence on AUC of all PPIs during fluvoxamine treatment. These findings suggest that CYP2C19 genotyping is not always a good indicator for estimating AUC of PPIs. Limited sampling strategies (LSS) were developed to estimate AUC simply and accurately. It is important to minimize the number of blood samples because of patient's acceptance. This article reviewed the usefulness of LSS for estimating AUC of three PPIs (omeprazole: OPZ, lansoprazole: LPZ and rabeprazole: RPZ). The best prediction formulas in each PPI were $AUC_{OPZ}=9.24\times C_{6h}+2638.03$, $AUC_{LPZ}=12.32\times C_{6h}+3276.09$ and $AUC_{RPZ}=1.39\times C_{3h}+7.17\times C_{6h}+344.14$, respectively. In order to optimize the sampling strategy of LPZ, we tried to establish LSS for LPZ using a time point within 3 hours through the property of pharmacokinetics of its enantiomers. The best prediction formula using the fewest sampling points (one point) was $AUC_{racemic\ LPZ}=6.5\times C_{3h}$ of (R)-LPZ$+13.7\times C_{3h}$ of (S)-LPZ$-9917.3\times$G1$-14387.2\times$G2$+7103.6$ (G1: homozygous extensive metabolizer is 1 and the other genotypes are 0; G2: heterozygous extensive metabolizer is 1 and the other genotypes are 0). Those strategies, plasma concentration monitoring at one or two time-points, might be more suitable for AUC estimation than reference to CYP2C19 genotypes, particularly in the case of coadministration of CYP mediators.

Key words——limited sampling strategy; omeprazole; lansoprazole; rabeprazole; cytochrome P450 (CYP) 2C19 (CYP2C19)

INTRODUCTION

The proton pump inhibitors (PPIs), which are specific for H^+, K^+-ATPase, inhibit the function of the proton pump responsible for the terminal step in gastric acid secretion. PPIs, such as omeprazole (OPZ), lansoprazole (LPZ) and rabeprazole (RPZ), are now widely used as the first-line acid inhibitors in Japan. The major indications of PPIs are acid-related diseases, such as the eradication of *Helicobacter pylori* (*H. pylori*), peptic ulcer, gastroesophageal reflux diseases (GERD), and Zollinger Ellison syndrome.[1)]

Information on genetic polymorphisms, including single nucleotide polymorphisms, found in the genes encoding drug-metabolizing enzymes, drug transporters and drug receptors are now applicable to tailor-made drug therapy.[2)] Hepatic drug oxidation is a major source of inter-individual variations in drug pharmacokinetics (PK) and therapeutic response. Cytochrome P450 (CYP) 2C19 (CYP2C19) genotype is regarded as a useful tool to predict area under the blood concentration-time curve (AUC) of PPIs because of the major contribution of CYP2C19 to OPZ, LPZ and RPZ metabolism.[3)] The genotypes of CYP2C19 are classified into the three groups, homozygous extensive metabolizer (hom-EM), heterozygous extensive metabolizer (het-EM), and poor metabolizer (PM).[4,5)] The acid suppressive effect of PPIs has been reported to correlate with AUC level.[6–8)] Therefore, AUC and intragastric pH during PPIs treatment in the hom-EM group are lowest, those in the het-EM group come next, and those in the PM group are highest of the three groups. These CYP2C19 genotype-dependent differences in PK and pharmacodynamics (PD) of PPIs influence the cure rates for the GERD and *H. pylori* infection by PPI-based therapies.[9,10)]

On the other hand, a number of reviews have presented conflicting evidence for or against the influence of PPIs-related CYP2C19 polymorphisms on eradication rates.[11)] Although several studies have shown the differences between hom-EM and PM genotypes in *H. pylori* eradication rates, there has not

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been a comprehensive inter-study summary that will confirm these differences and, in particular, explain the effect of the het-EM polymorphism on *H. pylori* eradication rates of first-line therapy. Moreover, it has been also reported that the antisecretory efficacy of various PPIs is affected by CYP2C19 polymorphisms to different degrees. OPZ is affected by CYP2C19 the most, and the effect of CYP2C19 polymorphisms on the antisecretory efficacy of LPZ and RPZ is smaller than that of OPZ.[3,12] Since CYP2C19-dependent pharmacogenetic differences are one of the main reasons for the failure of *H. pylori* eradication, first-line eradication therapy for *H. pylori* using LPZ or RPZ may decrease the failure rate. As just described, it is not clear whether newer PPIs used in first-line eradication therapies are affected by the CYP2C19 polymorphisms. Therefore, further studies are needed to clarify these issues.

The expression of individual P450 proteins in the liver is influenced by a number of factors, such as hepatic dysfunction, ageing, smoking, alcohol and drug-drug interaction as well as the polymorphisms. It is possible that an identification of CYP2C19 genotype alone is not sufficient to estimate PD based on AUC of PPIs in cases with decreased CYP2C19 activity. Therefore, CYP2C19 genotyping is not always a good indicator for estimating AUC of PPIs in patients with those factors. In some clinical settings, measurement of plasma concentrations of PPIs is essential to estimate its AUC.[13,14] To our knowledge, however, there have been no reports of a simple method that can dependably predict AUC of PPIs based on a few plasma concentrations.

The purpose of this study is to identify a single time-point to measure plasma concentrations of OPZ, LPZ and RPZ that adequately reflect AUC after a single administration of PPIs and with coadministration with clarithromycin (CAM), an inhibitor of CYP3A4,[15,16] and with fluvoxamine (FLU), an inhibitor of CYP2C19.[17,18]

ANALYTICAL METHODS

Study Design Eighteen (6 hom-EMs, 6 het-EMs and 6 PMs), 18 (6 hom-EMs, 6 het-EMs and 6 PMs) and 21 (7 hom-EMs, 7 het-EMs and 7 PMs) healthy Japanese volunteers, who were *H. pylori*-negative, were enrolled in OPZ study, LPZ (racemic- and enantiomers) study and RPZ study, respectively. The Ethics Committee of Hirosaki University School of Medicine approved this study protocol, and written informed consent had been obtained from each participant before any examinations. A randomized, double-blind, placebo-controlled, crossover study design in three phases was conducted at intervals of 2 weeks in each study. CAM, FLU or placebo was given orally twice a day for 6 days. Those volunteers within each group were allocated to each of the 3 different drug sequences: placebo-CAM-FLU (random order). On day 6, they took a single oral 40 mg dose of OPZ, 60 mg dose of LPZ or 20 mg dose of RPZ with 400 mg dose of CAM, 25 mg dose of FLU, or placebo after overnight fasting.

Genotyping The mutated alleles for CYP2C19, CYP2C19*3(*3), and CYP2C19*2(*2) had been identified using polymerase chain reaction-restriction fragment length polymorphism methods of De Morais *et al.* before this study.[19]

Blood Samplings and Assay Blood samplings for determination of concentrations of each PPI were taken into heparinized tubes just before and at 1, 1.5, 2, 3, 4, 6 and 8 hours after OPZ administration, before and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours after LPZ (racemic- and enantiomers) administration, and before and at 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24 hours after RPZ administration. Plasma concentrations of OPZ,[20] LPZ,[21] RPZ,[22] (R)- and (S)-LPZ[23] were quantified using high-performance liquid chromatography (HPLC). method developed in our laboratory.

Data Analyses AUC $(0-\infty)$ was calculated using the trapezoidal rule. Multiple linear regression analysis involves correlating the dependent variable (AUC) to the independent variables (concentrations at different time points; C_1, C_2 and C_n) *via* stepwise regression analysis. This analysis produced the following prediction formula:

$$AUC = B + A_1 \times C_1 + A_2 \times C_2 + \cdots + A_n \times C_n,$$

where B is an intercept and A_1, A_2 and A_n are fitted constants associated with each timed concentration.

THE EFFECTS OF CAM AND FLU AGAINST AUC OF PPIS

It is possible that PPIs interact with many drugs.[24] These findings suggest that CYP2C19 genotyping is not always a good indicator for estimating AUC of PPIs. We examined whether CAM and FLU would really affect the metabolism of each PPI in three different CYP2C19 genotypes.

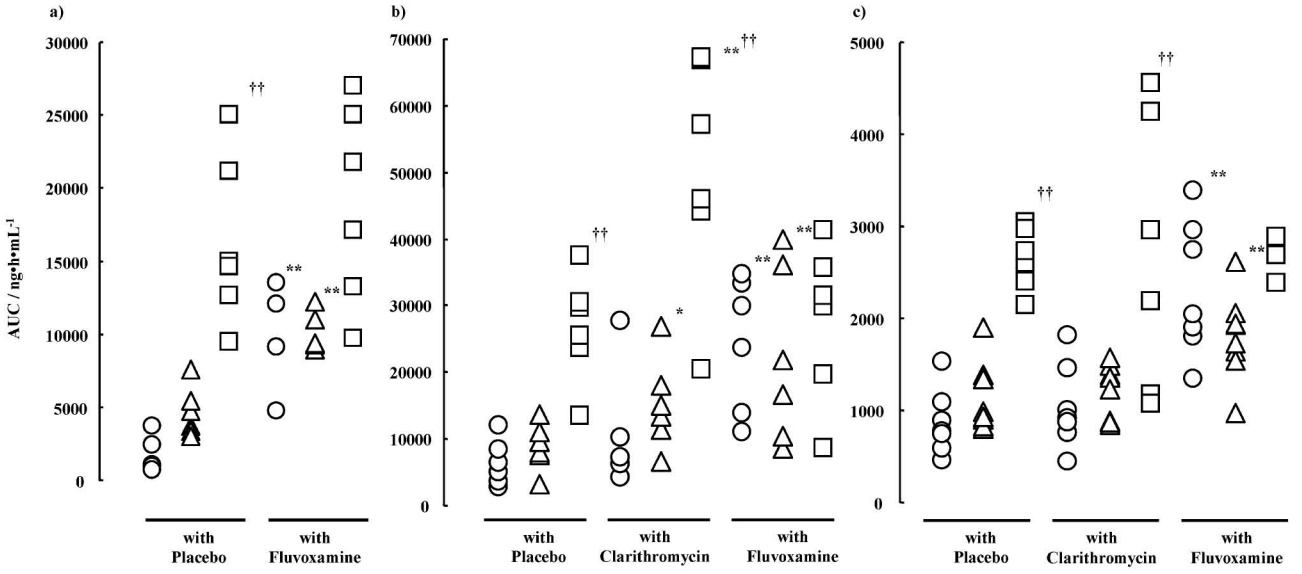

Fig. 1. Area under the Blood Concentration-time Curve (AUC) of Each Proton Pump Inhibitor during Placebo, CAM and FLU Treatment in hom-EM, het-EM, and PM of CYP2C19

a) omeprazole, b) lansoprazole and c) rabeprazole. ○ hom-EM, △ het-EM and □ PM. ††$p<0.01$ compared with hom-EM; the Mann-Whitney test after the Kruskal-Wallis test ($p<0.05$). *$p<0.05$ and **$p<0.01$ compared with the placebo treatment; the Wilcoxon test after the Friedman test ($p<0.05$).

As shown in Fig. 1, there were significant differences in the AUC of OPZ, LPZ and RPZ between hom-EM and PM ($p<0.05$) in the placebo treatment groups. And there were significant differences in the AUC of LPZ and RPZ between hom-EM and PM ($p<0.05$) in CAM treatment groups. On the other hand, there were no differences in AUC of all PPIs during FLU treatment among CYP2C19 genotypes. Compared with the placebo treatment groups, CAM treatment significantly increased the AUC of LPZ in het-EM ($p<0.05$) and in PM ($p<0.01$). On the other hand, CAM treatment did not affect the AUC of RPZ in each genotype group. FLU treatment significantly increased AUC of all PPIs in hom-EM ($p<0.01$, respectively) and in het-EM ($p<0.01$, respectively). On the other hand, FLU treatment did not affect AUC of all PPIs in PM.

The present study revealed that FLU coadministration masked the effects of CYP2C19 genotypes on AUC of all PPIs. On the other hand, the AUC of LPZ was increased by CAM compared with placebo; there was an especially large influence in PM. Thus, LPZ metabolism is affected by CYP3A as well as CYP2C19. Several *in vivo* studies have suggested that coadministration of CAM increases the plasma concentration of OPZ.[25] Therefore, identification of CYP2C19 genotype alone was sometimes insufficient to estimate AUC of PPIs in cases with decreased CYP2C19 activity or in the setting of such a drug-drug interaction.

LIMITED SAMPLING STRATEGIES FOR PPIS

PK parameters describe the effect of the body on the drug, whereas pharmacodynamics describe the effect of the drug on the body. AUC is the most commonly used PK parameter to characterize exposure to a drug. The main disadvantage of utilizing AUC is the number of samples required, often more than 10 over a dosing interval. Taking account of the time required for blood collection periods, the patients' burden and the cost of measuring plasma concentration, AUC measurement is not appropriate for therapeutic drug monitoring. Hence, it is clinically important that the prediction of AUC is calculated by limited blood samples from patients. The prediction of PK parameters from a limited blood sampling schedule (often with 3 or fewer concentrations) was proposed as a possible approach in the testing of new formulations. The benefits of a limited sampling strategy (LSS) are apparent, including reduced cost, labor and inconvenience, shorter hospital stay for patients, and faster turnover time for results.[26] Our objectives are to identify the common time-point to give a plasma concentration of PPIs that adequately reflects the AUC in a single administration of PPIs, and in co-administration with CAM and with FLU.[27,28]

Regarding the correlation of plasma concentrations of OPZ at various time points with the AUC of OPZ, the plasma concentrations of OPZ at 6 and 8 hours after administration (C_{6h} and C_{8h}) showed high correlation coefficients (r) (not less than 0.8, $p<0.001$) with the AUC of OPZ in coadministration with placebo and FLU (Table 1). In LPZ study, the correlations of C_{3h}, C_{4h}, C_{6h}, and C_{8h} with AUC showed high r (not less than 0.8, $p<0.001$) in coadministration with placebo, CAM, and FLU (Table 1). In RPZ study, the correlations of C_{5h}, C_{6h}, C_{8h}, C_{10h} and C_{12h} with AUC showed high r (not less than 0.7, $p<0.001$) in coadministration with placebo and CAM (Table 1). However, plasma concentrations of RPZ did not correlate well with the AUC of RPZ in co-administration with FLU.

The AUC was calculated based on all the data sets in multiple linear regression analysis of each PPI study. As shown in Table 2, the only sampling time common to these linear regressions was 6 h. The r^2 showed more than 0.8 in the linear regression using not less than two points in RPZ. The best prediction formulas in each PPIs were $AUC_{OPZ}=9.24\times C_{6h}+2638.03$, $AUC_{LPZ}=12.32\times C_{6h}+3276.09$ and $AUC_{RPZ}=1.39\times C_{3h}+7.17\times C_{6h}+344.14$, respectively.

ESTIMATION OF AUC OF THE RACEMIC LPZ BY USING LIMITED PLASMA CONCENTRATION OF LPZ ENANTIOMERS

The present study demonstrated that the AUC of LPZ can be estimated by one defined sampling time point of C_{6h}. However, we thought that 6 h is too long

Table 1. Correlation between Plasma OPZ, LPZ and RPZ Concentrations at Various Time Points and $AUC_{0-\infty}$ in Co-administration with Placebo, CAM and FLU

Sampling time /h	with Placebo			with Clarithromycin		with Fluvoxamine		
	OPZ ($n=18$)	LPZ ($n=18$)	RPZ ($n=21$)	LPZ ($n=18$)	RPZ ($n=21$)	OPZ ($n=18$)	LPZ ($n=18$)	RPZ ($n=21$)
1	0.163	0.375	−0.203	0.313	0.050	0.141	−0.086	−0.193
2	0.607*	0.694***	−0.128	0.893***	0.341	0.532*	0.628**	0.383
3	0.934***	0.889***	0.476*	0.915***	0.742***	0.644**	0.884***	0.677***
4	0.933***	0.934***	0.816***	0.973***	0.692***	0.528*	0.948***	0.440*
6	0.964***	0.940***	0.861***	0.992***	0.761***	0.887***	0.953***	0.273
8	0.953***	0.909***	0.900***	0.979***	0.825***	0.920***	0.905***	−0.193
12		0.783***	0.915***	0.940***	0.860***		0.853***	0.182
24		0.514*	0.438*	0.705***	0.924***		0.471*	0.165

Data are correlation coefficient (r); the Spearman's rank correlation test. * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Table 2. The Best Formulas in Each Number of Sample Point Derived Using All-subset (Co-administration with Placebo, CAM and FLU Treatments) Multiple Linear Regression Approach to Estimate the $AUC_{0-\infty}$

Number of sample point	Sampling time/h	formula for $AUC_{0-\infty}$	r^2	p
Omeprazole ($n=36$)				
1	6	$9.24\cdot C_{6h}+2638.03$	0.881	<0.001
2	2, 6	$1.53\cdot C_{2h}+8.26\cdot C_{6h}+954.43$	0.981	<0.001
3	1, 2, 6	$0.58\cdot C_{1h}+1.42\cdot C_{2h}+8.35\cdot C_{6h}+774.50$	0.984	<0.001
Lansoprazole ($n=54$)				
1	6	$12.32\cdot C_{6h}+3276.09$	0.928	<0.001
2	6, 12	$7.67\cdot C_{6h}+10.94\cdot C_{12h}+4944.11$	0.956	<0.001
3	2, 6, 12	$2.08\cdot C_{2h}+5.01\cdot C_{6h}+12.87\cdot C_{12h}+1263.23$	0.990	<0.001
Rabeprazole ($n=63$)				
1	6	$7.66\cdot C_{6h}+968.02$	0.496	<0.001
2	3, 6	$1.39\cdot C_{3h}+7.17\cdot C_{6h}+344.14$	0.825	<0.001
3	2, 3, 6	$1.11\cdot C_{2h}+1.23\cdot C_{3h}+7.85\cdot C_{6h}+158.38$	0.922	<0.001

C_n, omeprazole, lansoprazple and rabeprazole concentration ($ng\cdot ml^{-1}$) at a specified time point during placebo, clarithromycin and fluvoxamine; $AUC_{0-\infty}$, area under the concentration-time curve ($ng\cdot h\cdot ml^{-1}$) from 0 to infinity; r^2, coefficient of determination.

for outpatients to wait to be tested. LPZ possess asymmetric sulfur in its chemical structure and has been clinically used as a racemic mixture. Generally, the pharmacokinetics of enantiomers of chiral compounds differ in the human body. CYP2C19 had a greater influence on the disposition of (S)-LPZ than on the (R)-enantiomer. The R/S ratios for the AUC of LPZ for the hom-EMs, het-EMs and PMs were 12.7, 8.5 and 5.8, respectively.[29] Taking account of the practicality and convenience (*e.g.*, shorter time of prediction) in selecting the optimum sampling strategy, we investigated establishment of LSS for LPZ using time point within 3 h through the property of pharmacokinetics of enantiomers of chiral compounds.[30]

As shown in Fig. 2, in above data sets on LPZ study, the AUC of racemic LPZ correlated well with the AUC ratio of (R)- and (S)-LPZ as the fractional expression described below: AUC ratio of R/S-LPZ $=5.1+32530.1/$AUC of racemic LPZ ($r=0.799$, $p<0.001$). AUC, maximum drug concentration (C_{max}), the elimination half-life, and maximum drug concentration time (t_{max}) of (S)-LPZ were lower and shorter, respectively, than those of the corresponding (R)-enantiomer in all three treatments (data not shown). The best prediction formula using the fewest sampling points (one point) was AUC of racemic LPZ$=6.5\times C_{3h}$ of (R)-LPZ$+13.7\times C_{3h}$ of (S)-LPZ$-9917.3\times$G1$-14387.2\times$G2$+7103.6$ (G1: hom-EM was 1 and the other genotypes were 0; G2: het-EM was 1 and the other genotypes were 0) (Table 3). The only sampling time common to these multiple linear

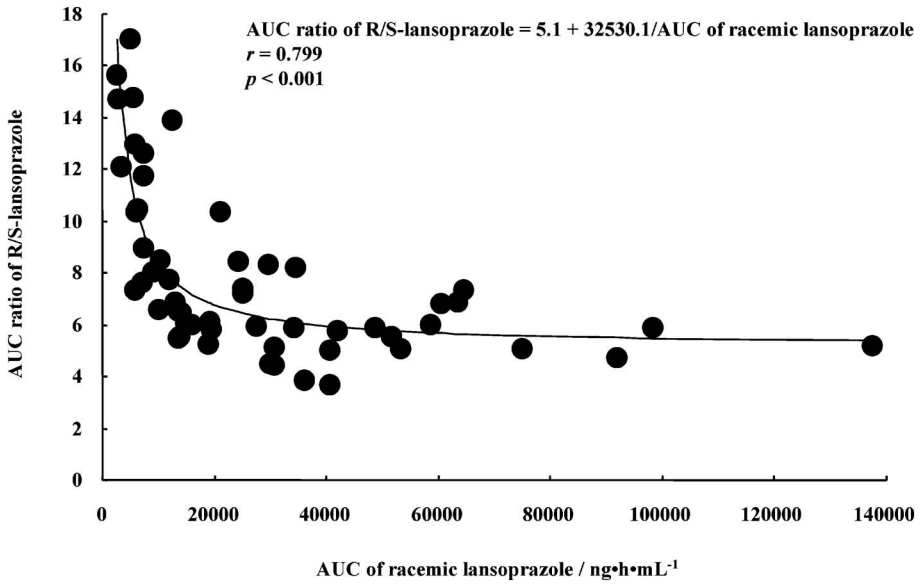

Fig. 2. Correlation between AUC of Racemic Lansoprazole and AUC ratio of R/S-Lansoprazole

Table 3. Best Formulas for Each Number of Sample Points Derived Using All-subset ($n=54$; Co-administration with Placebo ($n=18$), CAM ($n=18$) and FLU ($n=18$) Treatment) Multiple Linear Regression Approach to Estimate $AUC_{0-\infty}$ of Racemic Lansoprazole

Number of sampling points	Sampling time/h	Formula for $AUC_{0-\infty}$ of racemic lansoprazole	r^2	p
1	3†	$6.5\cdot$(R)-$C_{3h}+13.7\cdot$(S)-$C_{3h}-9917.3\cdot$G1$-14387.2\cdot$G2$+7103.6$	0.897	<0.001
	3	$3.6\cdot$(R)-$C_{3h}+20.5\cdot$(S)-$C_{3h}+1186.4$	0.858	<0.001
2	1, 3†	$3.6\cdot$(R)-$C_{1h}+3.0\cdot$(R)-$C_{3h}+18.4\cdot$(S)-$C_{3h}-9705.8\cdot$G1$-12851.3\cdot$G2$+7673.8$	0.930	<0.001
	1, 3	$3.9\cdot$(R)-$C_{1h}+0.01\cdot$(R)-$C_{3h}+25.1\cdot$(S)-$C_{3h}+2253.7$	0.898	<0.001
3	1, 1.5, 3†	$2.9\cdot$(R)-$C_{1h}+2.9\cdot$(S)-$C_{1.5h}+22.8\cdot$(S)-$C_{3h}-7645.7\cdot$G1$-10994.0\cdot$G2$+9014.4$	0.929	<0.001
	1, 1.5, 3	$2.6\cdot$(R)-$C_{1h}+3.2\cdot$(S)-$C_{1.5h}+24.1\cdot$(S)-$C_{3h}+1830.4$	0.903	<0.001

† CYP2C19 genotype is included into the formula for AUC of racemic lansoprazole. C_n, plasma concentration ($ng\cdot ml^{-1}$) of (R)- or (S)-lansoprazole at a specified time point within 3 h. G1, hom-EM was 1 and the others were 0; G2, het-EM was 1 and the others were 0. r^2, coefficient of determination.

regressions was 3 h in (S)-LPZ. We have demonstrated that the AUC of racemic LPZ can be estimated by using the plasma concentrations of both LPZ enantiomers at identical sampling times within 3 h, a shorter time frame.

CONCLUSION

Our results must be interpreted within the context of the study's limitations. This study was performed on a small number of healthy subjects following a single administration of PPIs. In addition, the developed prediction formula should be tested on a separate set of subject data. Therefore, further studies will be required to confirm whether or not AUC of PPIs determined based on LSS is clinically relevant after repeated doses. Moreover, we should confirm whether these regression equations are accurate or not in patients treated with a multiple-dose regimen of PPIs.

Chong *et al*. reported that the relationship between CYP2C19 genotype and clinical outcome after PPI therapy has not yet been clearly delineated.[31] In addition, recent meta-analysis has reported that PPIs therapy for *H. pylori* eradication is likely to be effective, irrespective of CYP2C19 genotype.[11] Unfortunately, plasma concentrations of PPIs were not measured in those studies. Therefore, PK-PD of PPIs is still contentious. CYP2C19 activity is decreased in the case of hepatic dysfunction as well as PPIs-FLU interaction.[13,14] Similarly, CYP2C19 activity is decreased in the elderly.[32,33] As shown above, only identification of CYP2C19 genotypes is sometimes insufficient for estimation of AUC of PPIs. To investigate the usefulness of CYP2C19 genotyping in PPI administration, PK-PD of PPIs should be estimated with combining genotypes and measured AUC values in future investigation. Interestingly, Furuta *et al*. reported that the C_{3h} of LPZ is a useful indicator of treatment effect in GERD patients.[34]

As shown in this study, plasma concentration monitoring at one or two time-points could be broadly applied as a method for AUC estimation after PPIs administration. Taking into account the correlation coefficients and prediction precisions, it is reasonable to conclude that C_{6h} was the best time point to estimate the AUC of OPZ, LPZ and RPZ. Additionally, C_{3h} of LPZ enantiomers is the most useful time point to estimate the AUC of racemic LPZ. LSS might be a suitable method for estimating AUC of these PPIs.

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