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A Randomized, 2-Period, Crossover Design Study to Assess the Effects of Dexlansoprazole, Lansoprazole, Esomeprazole, and Omeprazole on the Steady-State Pharmacokinetics and Pharmacodynamics of Clopidogrel in Healthy Volunteers

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Objectives The aim of this study was to assess the effects of different proton pump inhibitors (PPIs) on the steady-state pharmacokinetics and pharmacodynamics of clopidogrel.

Background Metabolism of clopidogrel requires cytochrome P450s (CYPs), including CYP2C19. However, PPIs may inhibit CYP2C19, potentially reducing the effectiveness of clopidogrel.

Methods A randomized, open-label, 2-period, crossover study of healthy subjects (n = 160, age 18 to 55 years, homozygous for CYP2C19 extensive metabolizer genotype, confined, standardized diet) was conducted. Clopidogrel 75 mg with or without a PPI (dexlansoprazole 60 mg, lansoprazole 30 mg, esomeprazole 40 mg, or, as a positive control to maximize potential interaction and demonstrate assay sensitivity, omeprazole 80 mg) was given daily for 9 days. Pharmacokinetics and pharmacodynamics were assessed on days 9 and 10. Pharmacodynamic endpoints were vasodilator-stimulated phosphoprotein $P2Y_{12}$ platelet reactivity index, maximal platelet aggregation to 5 and 20 μmol/l adenosine diphosphate, and VerifyNow P2Y12 platelet response units.

Results Pharmacokinetic and pharmacodynamic responses with omeprazole demonstrated assay sensitivity. The area under the curve for clopidogrel active metabolite decreased significantly with esomeprazole but not with dexlansoprazole or lansoprazole. Similarly, esomeprazole but not dexlansoprazole or lansoprazole significantly reduced the effect of clopidogrel on vasodilator-stimulated phosphoprotein platelet reactivity index. All PPIs decreased the peak plasma concentration of clopidogrel active metabolite (omeprazole > esomeprazole > lansoprazole > dexlansoprazole) and showed a corresponding order of potency for effects on maximal platelet aggregation and platelet response units.

Conclusions Generation of clopidogrel active metabolite and inhibition of platelet function were reduced less by the coadministration of dexlansoprazole or lansoprazole with clopidogrel than by the coadministration of esomeprazole or omeprazole. These results suggest that the potential of PPIs to attenuate the efficacy of clopidogrel could be minimized by the use of dexlansoprazole or lansoprazole rather than esomeprazole or omeprazole. (A Study of the Effects of Multiple Doses of Dexlansoprazole, Lansoprazole, Omeprazole or Esomeprazole on the Pharmacokinetics and Pharmacodynamics of Clopidogrel in Healthy Participants; NCT00942175) (J Am Coll Cardiol 2012;59:1304–11) © 2012 by the American College of Cardiology Foundation

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The co-administration of proton pump inhibitors (PPI) with clopidogrel reduces the risk for gastrointestinal bleeding associated with the antiplatelet effects of clopidogrel (1). There are conflicting data as to whether PPIs have the potential to reduce the effectiveness of clopidogrel (1). Clopidogrel is a prodrug that requires metabolism by hepatic cytochrome P450 (CYP) enzymes, including CYP2C19, to an active metabolite that blocks platelet $P2Y_{12}$ adenosine diphosphate (ADP) receptors. Because PPIs are known inhibitors of CYP2C19 (1), they may prevent the conversion of clopidogrel to its active metabolite ($clopidogrel_{AM}$). However, because not all PPIs inhibit CYP2C19 to the same extent (2–4), the potential for a clinically relevant drug-drug interaction with clopidogrel may not be generalized to all PPIs. The present randomized, open-label, 2-period, crossover study was therefore designed to determine the effects of 4 different PPIs (dexlansoprazole, lansoprazole, omeprazole, and esomeprazole) on the steady-state pharmacokinetics (PK) and pharmacodynamics (PD) of clopidogrel.

Methods

The study design, enrollment criteria, clopidogrel PK and PD, and statistics are described in detail in the Online Appendix. To eliminate variables known to influence clopidogrel and/or PPI metabolism, homozygous CYP2C19 extensive metabolizer genotype healthy subjects were enrolled and confined in a clinical research unit.

Results

Study population. The disposition of subjects is shown in Online Figure 1. Demographic characteristics of the 160 subjects who were randomized to receive study drug are shown in Table 1. One hundred fifty subjects completed study drug and all study visits (Online Fig. 1).

PK of clopidogrel in the presence and absence of PPIs. Clinically relevant daily doses of clopidogrel (75 mg), dexlansoprazole (60 mg), lansoprazole (30 mg), and esomeprazole (40 mg) were used, and the timing of PPI dosing relative to clopidogrel was adjusted to synchronize times to reach peak concentration. Omeprazole 80 mg/day, a potent inhibitor of CYP2C19, was used as a positive control for the interaction of a PPI with clopidogrel PK. As expected, peak plasma concentration of $clopidogrel_{AM}$ and area under the plasma concentration–time curve (AUC_t) were lower when clopidogrel was administered with omeprazole 80 mg compared with clopidogrel alone (Table 2, Figs. 1B and 1D).

$Clopidogrel_{AM}$ AUC_t on day 9 of the administration of clopidogrel with dexlansoprazole or lansoprazole was similar to that observed on day 9 of the administration of clopidogrel alone (Table 2, Fig. 1). In contrast, $clopidogrel_{AM}$ AUC_t on day 9 of the administration of clopidogrel with esomeprazole was reduced compared with that observed at 9 days of the administration of clopidogrel alone (Fig. 1B, Table 2).

Relative to clopidogrel alone, all PPIs decreased the peak plasma concentration of $clopidogrel_{AM}$ (omeprazole > esomeprazole > lansoprazole > dexlansoprazole) (Figs. 1C and 1D).

Clopidogrel was rapidly absorbed (median time to reach peak concentration for intact clopidogrel 1 h), and this was unaffected by lansoprazole, dexlansoprazole, omeprazole, or esomeprazole (data not shown).

Abbreviations and Acronyms

ADP = adenosine diphosphate
AUC_t = area under the plasma concentration–time curve
$clopidogrel_{AM}$ = clopidogrel active metabolite
CYP = cytochrome P450
HPR = high on-treatment platelet reactivity
MPA = maximal platelet aggregation
PD = pharmacodynamics
PK = pharmacokinetics
PPI = proton pump inhibitor
PRI = platelet reactivity index
PRU = platelet response units
VASP = vasodilator-stimulated phosphoprotein

PD of clopidogrel in the presence and absence of PPIs. Omeprazole 80 mg, the positive control, when coadministered with clopidogrel, caused significant changes in vasodilator-stimulated phosphoprotein (VASP) platelet reactivity index (PRI), light transmission aggregation maximal platelet aggregation (MPA), and VerifyNow P2Y12 (Accumetrics, Inc., San Diego, CA) platelet response units (PRU) compared with clopidogrel alone (Figs. 2, 3, and 4, Tables 3, 4, and 5).

VASP $P2Y_{12}$ ASSAY. The least squares mean differences in VASP PRI 24 h after 9 days administration of clopidogrel with lansoprazole or clopidogrel with dexlansoprazole compared with clopidogrel alone were small (4.1% and 2.0%, respectively) with 90% confidence interval upper boundaries <15% (Table 3, Fig. 2), that is, less than the pre-specified upper no-effect boundary. In contrast, the difference in VASP PRI 24 h after 9 days administration of clopidogrel with esomeprazole compared with clopidogrel alone was larger, 11.4%, and its 90% confidence interval upper boundary, 15.71%, extended beyond the upper no-effect boundary of 15% (Table 3, Fig. 2). The magnitude of the change in VASP PRI with esomeprazole (11.4%) was similar to that observed with omeprazole (11.0%).

LIGHT TRANSMISSION AGGREGATION. MPA in response to ADP 5 μmol/l 24h after 9 days coadministration of clopidogrel with dexlansoprazole was not significantly different from MPA after clopidogrel alone. As with dexlansoprazole, the difference in MPA after clopidogrel with lansoprazole compared with clopidogrel alone was also small but, unlike that with dexlansoprazole, was statistically significant. Similar results for both dexlanso-

and is a research collaborator with PLx Pharma and Takeda and served as the Chair of the COGENT trial. Dr. Michelson has been a member of the data safety monitoring boards of clinical trials sponsored by Eli Lilly/Daiichi Sankyo and Sanofi Aventis/Bristol-Myers Squibb. All other authors have reported that they have no relationship relevant to the contents of this paper to disclose.

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Table 1 Summary of Demographic and Baseline Characteristics for All PPI Groups

Characteristic	PPI Group 1: Lansoprazole (n = 40)	PPI Group 2: Dexlansoprazole (n = 40)	PPI Group 3: Omeprazole (n = 40)	PPI Group 4: Esomeprazole (n = 160)	Overall
Sex					
Male	20 (50.0%)	20 (50.0%)	20 (50.0%)	20 (50.0%)	80 (50.0%)
Female	20 (50.0%)	20 (50.0%)	20 (50.0%)	20 (50.0%)	80 (50.0%)
Age (yrs)	32.8 ± 6.48 (20–47)	35.7 ± 7.92 (22–53)	34.0 ± 7.40 (22–51)	33.3 ± 7.10 (20–49)	33.9 ± 7.26 (20–53)
Race					
White	40 (100.0%)	39 (97.5%)	39 (97.5%)	39 (97.5%)	157 (98.1%)
American Indian or Alaska Native	0	0	1 (2.5%)	1 (2.5%)	2 (1.3%)
Native Hawaiian or Other Pacific Islander	0	1 (2.5%)	0	0	1 (0.6%)
Ethnicity					
Hispanic or Latino	40 (100.0%)	38 (95.0%)	38 (95.0%)	40 (100.0%)	156 (97.5%)
Not Hispanic or Latino	0	2 (5.0%)	2 (5.0%)	0	4 (2.5%)
Weight (kg)	70.1 ± 10.29	70.8 ± 9.95	68.6 ± 7.44	71.6 ± 10.83	70.3 ± 9.69
Height (cm)	164.3 ± 8.91	165.0 ± 8.49	162.3 ± 8.40	164.3 ± 8.73	163.9 ± 8.61
BMI (kg/m^2)	25.9 ± 2.26	26.0 ± 2.41	26.1 ± 2.16	26.4 ± 2.50	26.1 ± 2.32

Values are n (%) or mean ± SD (range).
BMI = body mass index; PPI = proton pump inhibitor.

prazole and lansoprazole were observed when ADP 20 μmol/l was used as the agonist for platelet aggregation (Table 4). In contrast, the coadministration of esomeprazole with clopidogrel led to larger increases in ADP 5 μmol/l MPA, which was similar to the least squares mean difference observed with versus without the positive control, omeprazole (Table 4). Likewise, large, numerically similar differences were seen for both omeprazole and esomeprazole when ADP 20 μmol/l was used as the agonist for platelet aggregation (Table 4). Similar results were obtained analyzing the percent inhibition of platelet aggregation (Table 4).

VERIFYNOW P2Y12 ASSAY. Compared with clopidogrel alone, the increases in PRU when clopidogrel was coadministered with dexlansoprazole, lansoprazole, omeprazole, or esomeprazole were statistically significant; however, these changes were greatest for omeprazole and esomeprazole compared with dexlansoprazole and lansoprazole (Table 5). Results using VerifyNow P2Y12 percent inhibition to assess the effect of clopidogrel with and without PPIs were similar to results obtained using PRU (Online Table 5).

HIGH ON-TREATMENT PLATELET REACTIVITY (HPR). The frequency of HPR as defined by the recommended cutoffs

Table 2 Clopidogrel$_{AM}$ Pharmacokinetics With and Without PPIs

Variable	Clopidogrel With PPI	Clopidogrel Alone	Ratio*	90% CI
Lansoprazole 30 mg				
Tmax (h)	0.50 ± 0.50/4.00 (38)	0.50 ± 0.50/1.50 (38)		
C_{max} (ng/ml)	30.01 ± 15.26 (38)	39.14 ± 12.55 (38)	0.70	0.611–0.803
AUC_t (ng · h/ml)	36.42 ± 10.82 (38)	41.69 ± 10.02 (38)	0.86	0.802–0.916
Dexlansoprazole 60 mg				
Tmax (h)	0.50 ± 0.50/1.50 (36)	0.50 ± 0.50/1.50 (36)		
C_{max} (ng/ml)	29.33 ± 12.4 (36)	38.85 ± 15.7 (36)	0.73	0.652–0.827
AUC_t (ng · h/ml)	37.75 ± 13.13 (36)	41.25 ± 14.69 (36)	0.91	0.857–0.967
Esomeprazole 40 mg				
Tmax (h)	0.50 ± 0.50/1.50 (38)	0.50 ± 0.50/1.50 (38)		
C_{max} (ng/ml)	24.69 ± 10.64 (38)	40.97 ± 22.91 (38)	0.68	0.506–0.909
AUC_t (ng · h/ml)	31.23 ± 9.94 (38)	42.35 ± 18.79 (38)	0.84	0.644–1.093
Omeprazole 80 mg				
Tmax (h)	0.50 ± 0.50/3.00 (38)	0.50 ± 0.50/1.00 (38)		
C_{max} (ng/ml)	22.55 ± 10.68 (38)	38.25 ± 12.46 (38)	0.56	0.488–0.635
AUC_t (ng · h/ml)	26.28 ± 8.80 (38)	37.78 ± 12.04 (38)	0.69	0.644–0.749

Values are median ± minimum/maximum (n) for Tmax and mean ± SD (n) for C_{max} and AUC_t. *Point estimates for ratios of the central values for the natural logarithms of C_{max} and AUC_t. The pre-specified lower no-effect boundary limit for the 90% CI of the ratio was 0.80, and the upper no-effect boundary limit was 1.25.
AUC_t = area under the plasma concentration–time curve; CI = confidence interval; clopidogrel$_{AM}$ = clopidogrel active metabolite; C_{max} = peak plasma concentration; PPI = proton pump inhibitor; Tmax = time to reach peak concentration.

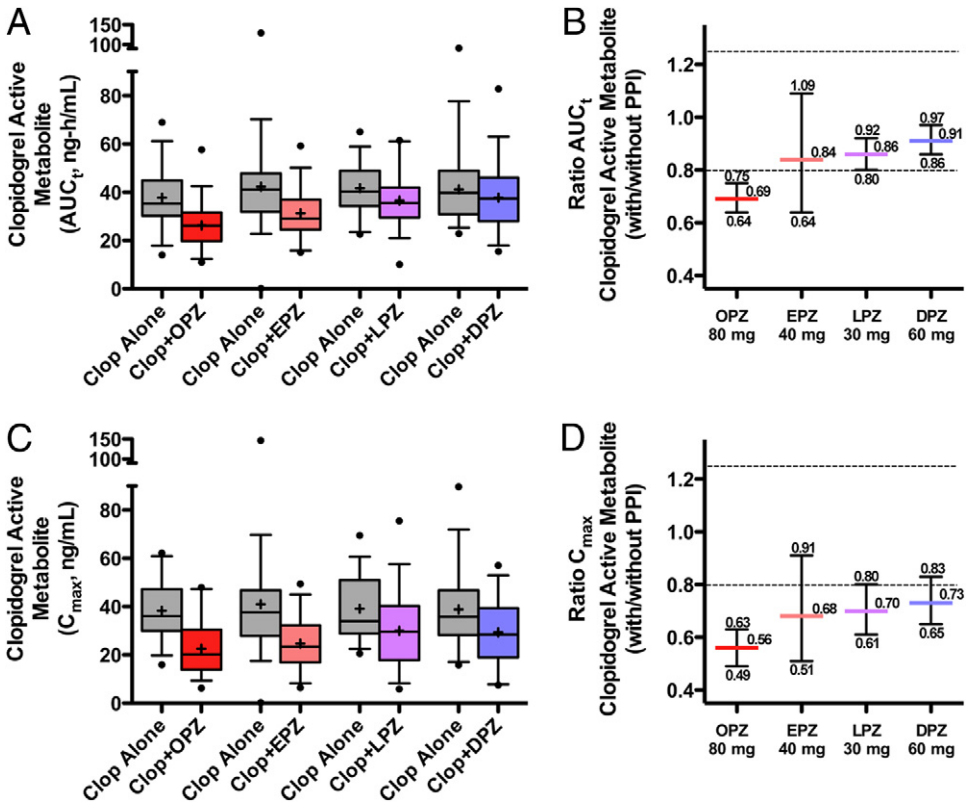

Figure 1 **Pharmacokinetics of Clopidogrel$_{AM}$**

Mean **(plus symbol)**, median **(bar)**, and 5th **(lower whisker)**, 25th **(lower boundary of box)**, 75th **(upper boundary of box)**, and 95th **(upper whisker)** percentiles for area under the plasma concentration–time curve (AUC_t) **(A)** and peak plasma concentration (C_{max}) **(C)** of the active metabolite of clopidogrel (clopidogrel$_{AM}$). **(B,D)** Ratios of the central values with and without proton pump inhibitors and corresponding 90% confidence intervals. **Dashed lines** represent 0.80 and 1.25 no-effect boundaries. Clop = clopidogrel; DPZ = dexlansoprazole; EPZ = esomeprazole; LPZ = lansoprazole; OPZ = omeprazole.

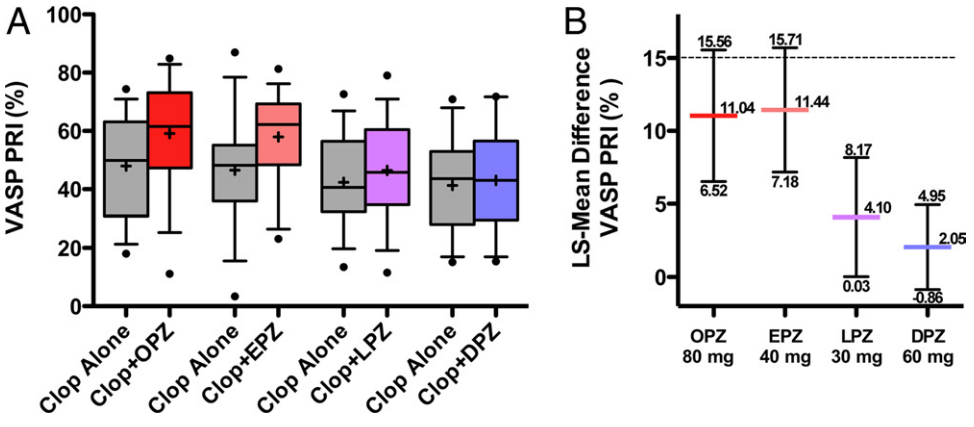

Figure 2 **Pharmacodynamics: VASP P2Y$_{12}$ PRI**

(A) Vasodilator-stimulated phosphoprotein (VASP) platelet reactivity index (PRI) (box and whisker limits as in Fig. 1). **(B)** Least squares (LS) mean differences with and without proton pump inhibitors and corresponding 90% confidence intervals. **Dashed line** represents upper no-effect boundary. Abbreviations as in Figure 1.

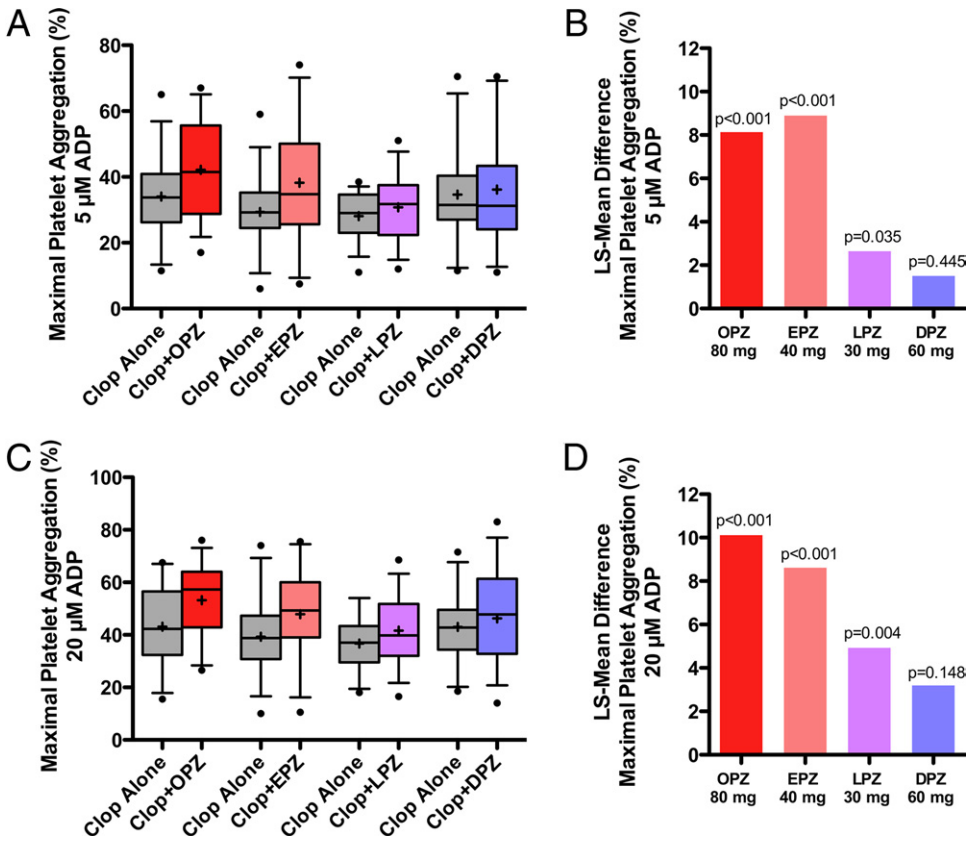

Figure 3 **Pharmacodynamics: Light Transmission Aggregation in Response to 5 and 20 μmol/l ADP**

Maximal platelet aggregation with 5 μmol/l **(A)** and 20 μmol/l **(B)** adenosine diphosphate (ADP) (box and whisker limits as in Fig. 1).
(B,D) Least squares (LS) mean differences with and without proton pump inhibitors. Abbreviations as in Figure 1.

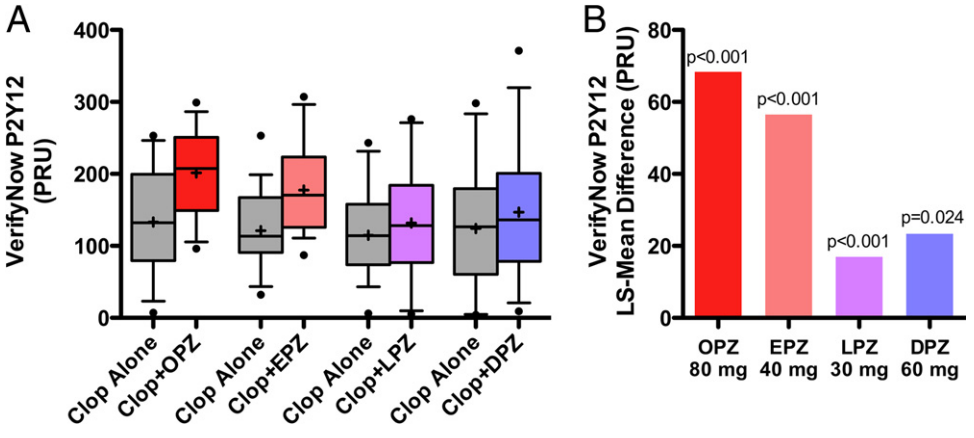

Figure 4 **Pharmacodynamics: Whole-Blood Platelet Aggregation by VerifyNow P2Y12 PRU**

(A) VerifyNow P2Y12 platelet response units (PRU) (box and whisker limits as in Fig. 1).
(B) Least squares (LS) mean differences with and without proton pump inhibitors. Abbreviations as in Figure 1.

Table 3 VASP $P2Y_{12}$ PRI in Clopidogrel-Treated Subjects With and Without 9 Days of PPI Coadministration

	PRI (%)			
PPI Group	Clopidogrel Alone	Clopidogrel Plus PPI	LS Mean Difference	90% CI of Difference
Lansoprazole 30 mg	42.3 ± 14.6	46.4 ± 16.4	4.1	0.03 to 8.17
Dexlansoprazole 60 mg	41.3 ± 15.4	43.0 ± 16.5	2.0	−0.86 to 4.95
Esomeprazole 40 mg	46.5 ± 17.3	58.0 ± 14.6	11.4	7.18 to 15.71
Omeprazole 80 mg	47.9 ± 15.7	59.1 ± 17.9	11.0	6.52 to 15.56

Values are mean ± SD. An LS mean difference with a 90% CI upper boundary of >15% was pre-specified to be significant.
LS = least squares; PRI = platelet reactivity index; VASP = vasodilator-stimulated phosphoprotein; other abbreviations as in Tables 1 and 2.

(5) of VASP PRI >50%, MPA 5 μmol/l ADP >46%, and PRU ≥236 was not significantly different 24 h after 9 days administration of clopidogrel with lansoprazole or dexlansoprazole compared with the administration of clopidogrel alone (Table 6). In contrast, 24 h after 9 days administration of clopidogrel with omeprazole, HPR by VASP PRI and VerifyNow P2Y12 PRU was significantly increased and, by MPA, approached significance compared with that after clopidogrel alone. Additionally, HPR as defined by VASP and MPA 5 μmol/l ADP was significantly greater 24 h after 9 days administration of clopidogrel with esomeprazole than after clopidogrel alone (Table 6).

Discussion

The main PK findings are as follows. 1) The study design and assay methods were appropriate to detect the effects of PPIs on clopidogrel PK parameters, as evidenced by significant effects of coadministered omeprazole 80 mg. 2) $Clopidogrel_{AM}$ AUC_t values were equivalent when clopidogrel was coadministered with or without dexlansoprazole 60 mg or lansoprazole 30 mg, whereas $clopidogrel_{AM}$ AUC_t values were decreased when clopidogrel was coadministered with omeprazole 80 mg or esomeprazole 40 mg compared with clopidogrel alone. 3) All tested PPIs significantly decreased peak plasma concentrations of $clopidogrel_{AM}$, but esomeprazole and omeprazole did so to a greater degree than lansoprazole and dexlansoprazole. 4) $Clopidogrel_{AM}$ times to reach peak concentration were not altered by any of the PPIs tested.

The main PD findings of this study are as follows. 1) The study design and assay methods were appropriate to detect the effects of PPIs on clopidogrel PD parameters, as evidenced by significant effects of coadministered omeprazole 80 mg on

Table 4 Platelet Aggregation Measured by Light Transmission Aggregometry in Response to 5 and 20 μmol/l ADP in Clopidogrel-Treated Subjects With and Without 9 Days PPI Coadministration

PPI Group	Clopidogrel Alone	Clopidogrel Plus PPI	LS Mean Difference	
MPA (%)				p value
ADP 5 μmol/l				
Lansoprazole 30 mg	28.1 ± 6.76	30.8 ± 9.35	2.6	0.035
Dexlansoprazole 60 mg	34.6 ± 14.23	36.2 ± 16.87	1.5	0.445
Esomeprazole 40 mg	29.3 ± 10.41	38.2 ± 17.77	8.9	<0.001
Omeprazole 80 mg	34.2 ± 12.32	42.5 ± 14.74	8.3	<0.001
ADP 20 μmol/l				
Lansoprazole 30 mg	36.7 ± 9.11	41.6 ± 12.65	4.9	0.004
Dexlansoprazole 60 mg	43.1 ± 13.24	46.3 ± 16.93	3.2	0.148
Esomeprazole 40 mg	39.3 ± 13.22	47.9 ± 15.77	8.6	<0.001
Omeprazole 80 mg	43.5 ± 14.00	53.5 ± 13.75	10.0	<0.001
IPA (%)				Percent change*
ADP 5 μmol/l				
Lansoprazole 30 mg	64.2 ± 9.19	59.5 ± 12.89	4.7	7.24
Dexlansoprazole 60 mg	54.0 ± 21.12	53.9 ± 22.57	0.1	0.22
Esomeprazole 40 mg	60.9 ± 14.60	49.3 ± 24.43	11.7	19.2
Omeprazole 80 mg	57.1 ± 14.40	44.2 ± 18.58	12.9	22.5
ADP 20 μmol/l				
Lansoprazole 30 mg	53.6 ± 11.89	46.0 ± 18.30	7.7	14.3
Dexlansoprazole 60 mg	43.2 ± 19.87	41.6 ± 23.26	1.6	3.69
Esomeprazole 40 mg	49.6 ± 17.42	38.7 ± 20.78	10.9	21.9
Omeprazole 80 mg	45.2 ± 17.16	32.8 ± 17.82	12.5	27.7

Values are as mean ± SD. *Calculated from LS means, which are provided in Online Table 7.
IPA = inhibition of platelet aggregation; MPA = maximal platelet aggregation; other abbreviations as in Tables 1 and 2.

Table 5 Platelet Aggregation Measured by VerifyNow P2Y12 PRU in Clopidogrel-Treated Subjects With and Without 9 Days of PPI Coadministration

	PRU			
PPI Group	Clopidogrel Alone	Clopidogrel Plus PPI	LS Mean Difference	p Value
Lansoprazole 30 mg	114.9 ± 56.4	131.8 ± 71.3	17.0	<0.001
Dexlansoprazole 60 mg	124.2 ± 79.1	146.7 ± 84.4	23.4	0.024
Esomeprazole 40 mg	121.1 ± 50.6	177.6 ± 55.4	56.5	<0.001
Omeprazole 80 mg	133.0 ± 67.6	201.5 ± 59.6	68.4	<0.001

Values are mean ± SD.
PRU = platelet reactivity units; other abbreviations as in Tables 1 and 3.

clopidogrel inhibition of VASP PRI, light transmission aggregation MPA, and VerifyNow P2Y12 PRU. 2) VASP PRI values were not different when clopidogrel was coadministered with or without dexlansoprazole or lansoprazole, whereas VASP PRI values were greater than the pre-specified no-effect limit when clopidogrel was coadministered with omeprazole or esomeprazole. 3) The coadministration of dexlansoprazole did not have a significant effect on MPA, while the coadministration of lansoprazole had a small effect on MPA, numerically similar to that of dexlansoprazole but statistically significant compared with that of clopidogrel alone. In contrast, omeprazole and esomeprazole had larger, numerically similar, highly significant effects on MPA. 4) All PPIs tested significantly reduced clopidogrel inhibition of VerifyNow P2Y12 PRU. However, the magnitudes of the effects of dexlansoprazole or lansoprazole on VerifyNow P2Y12 PRU were approximately one-third as large as the effects of omeprazole or esomeprazole.

By 3 distinct platelet function assays, the frequency of subjects who would be categorized as at risk for ischemic or thrombotic events after percutaneous coronary intervention using the consensus group cutoffs (5) was unchanged by the coadministration of dexlansoprazole or lansoprazole with clopidogrel but increased by the coadministration of omeprazole or esomeprazole with clopidogrel (Table 6).

In addition to a drug-drug interaction via CYP2C19, it has been proposed that PPIs may induce drug interactions by elevating gastric pH and altering drug absorption rates (1). The present study demonstrates that the rapid absorption of clopidogrel is unaffected by lansoprazole, dexlansoprazole, omeprazole, or esomeprazole.

Study strengths. This study's randomized, 2-period, crossover design was a strength, as were enrollment criteria eliminating variables known to influence clopidogrel and/or PPI metabolism, including CYP2C19 polymorphisms and provided a uniform study population. Subjects were confined and received a standardized, restricted diet, eliminating potential confounding factors (including smoking, concurrent medications, and noncompliance with drug administration). Finally, the study was well powered to detect both PK and PD effects, as demonstrated by the statistically significant effects of the positive control (omeprazole 80 mg).

Study limitations. Results for omeprazole 80 mg do not necessarily apply to the more commonly used doses of 20 and 40 mg. Also, this study was conducted in confined healthy volunteers, not patients, because this enabled us to use a randomized, crossover design while controlling for concurrent medications, diet, smoking, exercise, and other factors. Last, for uniformity, this study included only

Table 6 Change in HPR Status After the Coadministration of PPIs With Clopidogrel Compared With the Administration of Clopidogrel Alone

PPI Group	n	Subjects With HPR Converted to LPR After PPI Treatment	Subjects With LPR Converted to HPR After PPI Treatment	p Value*
HPR = VASP PRI >50%				
Dexlansoprazole 60 mg	36	5	4	1.000
Lansoprazole 30 mg	38	2	6	0.289
Esomeprazole 40 mg	38	3	13	0.021
Omeprazole 80 mg	38	3	12	0.035
HPR = MPA 5 μmol/l ADP>46%				
Dexlansoprazole 60 mg	36	1	4	0.375
Lansoprazole 30 mg	38	0	2	0.500
Esomeprazole 40 mg	38	0	11	0.001
Omeprazole 80 mg	37	3	11	0.057
HPR = PRU ≥236				
Dexlansoprazole 60 mg	36	0	2	0.500
Lansoprazole 30 mg	38	0	2	0.500
Esomeprazole 40 mg	38	0	5	0.062
Omeprazole 80 mg	38	1	13	0.002

*Exact p values calculated from binomial for numbers of discordant pairs.
HPR = high on-treatment platelet reactivity; LPR = low on-treatment platelet reactivity; other abbreviations as in Tables 1, 3, 4, and 5.

homozygous CYP2C19 wt/wt extensive metabolizers; consequently, our conclusions are limited to this population.

Conclusions

In this randomized, open-label, 2-period, crossover study of healthy subjects, generation of clopidogrel$_{AM}$ and inhibition of platelet function were reduced less by the coadministration of dexlansoprazole or lansoprazole with clopidogrel than by the coadministration of esomeprazole or omeprazole. These results suggest that the potential of PPIs to attenuate clopidogrel efficacy could be minimized by the use of dexlansoprazole or lansoprazole rather than esomeprazole or omeprazole.

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REFERENCES

1. Abraham NS, Hlatky MA, Antman EM, et al. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. J Am Coll Cardiol 2010;56:2051–66.
2. Karol MD, Locke CS, Cavanaugh JH. Lack of pharmacokinetic interaction between lansoprazole and intravenously administered phenytoin. J Clin Pharmacol 1999;39:1283–9.
3. Lefebvre RA, Flouvat B, Karolac-Tamisier S, Moerman E, Van GE. Influence of lansoprazole treatment on diazepam plasma concentrations. Clin Pharmacol Ther 1992;52:458–63.
4. Vakily M, Lee RD, Wu J, Gunawardhana L, Mulford D. Drug interaction studies with dexlansoprazole modified release (TAK-390MR), a proton pump inhibitor with a dual delayed-release formulation: results of four randomized, double-blind, crossover, placebo-controlled, single-centre studies. Clin Drug Invest 2009; 29:35–50.
5. Bonello L, Tantry US, Marcucci R, et al. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. J Am Coll Cardiol 2010;56:919–33.

Key Words: clopidogrel ■ drug-drug interaction ■ pharmacology ■ platelets ■ proton pump inhibitor ■ thrombosis.

APPENDIX

For an expanded Methods section and supplementary tables and figures and their legends, please see the online version of this article.