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CLINICAL RESEARCH

Effects of rabeprazole on the antiplatelet effects and pharmacokinetics of clopidogrel in healthy volunteers

Étude pharmacodynamique et pharmacocinétique de l'interaction entre le rabéprazole et le clopidogrel chez le volontaire sain

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Abbreviations: ADP, adenosine diphosphate; CYP, cytochrome P-450; EM, extensive metabolizer; IPA, inhibition of platelet aggregation; MFI, mean fluorescence intensity; MPA, maximal platelet aggregation; PGE1, prostaglandin E1; PPI, proton-pump inhibitors; PRI, platelet reactivity index; VASP, vasodilator-stimulated phosphoprotein.

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KEYWORDS
Clopidogrel;
CYP2C19 protein;
Drug interactions;
Proton-pump inhibitors;
Vasodilator-stimulated phosphoprotein

Summary
Background. — Several studies have suggested that proton-pump inhibitors (PPIs), mostly omeprazole, interact with clopidogrel efficacy by inhibiting the formation of its active metabolite *via* CYP2C19 inhibition. Whether this occurs with all PPIs is a matter of debate. As rabeprazole is a less potent CYP2C19 inhibitor than other PPIs, we studied the interaction between rabeprazole and the antiplatelet actions and pharmacokinetics of clopidogrel.
Aim. — To demonstrate the non-inferiority of rabeprazole over placebo using change in platelet reactivity index (PRI; vasodilator-stimulated phosphoprotein [VASP] assay) in a predefined population of good clopidogrel responders. Omeprazole was used as the positive control.
Methods. — In this randomized three-period crossover study in healthy volunteers, 36 healthy men received clopidogrel (75 mg/day for 7 days) with placebo, omeprazole (20 mg/day) or rabeprazole (20 mg/day). Clopidogrel antiplatelet effects and disposition kinetics were assessed on day 7 of combination therapy. Non-inferiority threshold was predefined as an upper limit of the 90% confidence interval for the difference in change in PRI between placebo and rabeprazole of < 10% in good clopidogrel responders.
Results. — In good clopidogrel responders (inhibition of VASP index > 30%), the clopidogrel antiplatelet effect remained non-inferior to placebo during rabeprazole (difference 3.4% [−1.7; 8.5]) but not omeprazole (difference 7.5% [2.5; 12.6]) co-administration. The AUC_{0-24} and C_{max} of active clopidogrel metabolite decreased with both omeprazole and rabeprazole, and conditions of bioequivalence were not met, except for AUC_{0-24} with rabeprazole.
Conclusions. — Rabeprazole does not interact with clopidogrel to the same extent as omeprazole. However, under our experimental conditions and proton-pump inhibitor doses, there was no significant pharmacodynamic interaction between rabeprazole or omeprazole and clopidogrel, despite a significant decrease in the formation of clopidogrel active metabolite.

MOTS CLÉS
Clopidogrel ;
CYP2C19 ;
Interactions médicamenteuses ;
Inhibiteurs de pompes à protons ;
Protéine VASP

Résumé
Contexte. — Plusieurs études, principalement menées avec l'oméprazole, ont suggéré une interaction entre inhibiteurs de la pompe à protons (IPPs) et clopidogrel, via l'inhibition du CYP2C19 impliqué dans la transformation de la pro-drogue clopidogrel en metabolite actif. L'importance de cette interaction avec les autres inhibiteurs de pompes à protons est discutée. Cette étude avait pour objectif l'analyse de l'interaction pharmacodynamique et pharmacocinétique entre le rabéprazole, un inhibiteur plus faible du CYP2C19 que l'oméprazole, et le clopidogrel.
Objectif. — L'objectif primaire était de démontrer la non-infériorité du rabéprazole par comparaison au placebo en utilisant l'index de réactivité plaquettaire (test VASP) dans une population de volontaires sains bon répondeurs au clopidogrel. L'oméprazole a été utilisé comme contrôle positif.
Méthodes. — Étude croisée, randomisée, en trois périodes, menée chez 36 hommes volontaires sains recevant du clopidogrel (75 mg/jour pendant 7 jours) avec du placebo, de l'oméprazole (20 mg/jour) ou du rabéprazole (20 mg/jour). L'effet anti-plaquettaire du clopidogrel et ses données pharmacocinétiques ont été mesurés au 7^{e} jour de traitement. Le seuil de non-infériorité a été défini a priori comme une limite supérieure de l'intervalle de confiance à 90 % < 10 % pour la différence entre la diminution de l'index de réactivité plaquettaire (test VASP) entre le placebo et le rabéprazole chez les bons répondeurs au clopidogrel.
Résultats. — Dans le groupe de bons répondeurs (inhibition du VASP PRI > 30 %), l'effet antiplaquettaire du clopidogrel était non inférieur à celui du placebo avec le rabéprazole (différence 3,4 % [−1,7; 8,5]) contrairement à l'oméprazole (différence 7,5 % [2,5; 12,6]). Toutefois, l'AUC_{0-24} et la C_{max} du métabolite actif du clopidogrel étaient significativement diminuées avec l'oméprazole et le rabéprazole et les conditions de bioéquivalence n'étaient pas remplies, excepté pour l'AUC_{0-24} avec le rabéprazole.
Conclusions. — L'interaction pharmacodynamique entre le rabéprazole et le clopidogrel n'a pas le même degré d'intensité que celle entre l'oméprazole et le clopidogrel. Cependant, dans nos conditions expérimentales, l'interaction entre rabéprazole ou oméprazole et le clopidogrel n'était pas significative malgré une inhibition significative de la génération du métabolite actif du clopidogrel.

Background

Dual antiplatelet therapy with aspirin and clopidogrel is associated with a significant reduction in cardiovascular ischemic events after acute coronary syndromes or percutaneous coronary interventions and is recommended in guidelines from the USA [1] and Europe [2]. Clopidogrel is an inactive prodrug that undergoes two oxidative steps involving multiple cytochrome P-450 (CYP) enzymes in its bioactivation to its pharmacologically active metabolite. Among them, CYP2C19, a CYP enzyme whose activity is determined genetically, contributes predominantly to this bioactivation [3,4] and modulates the antiplatelet and therapeutic response to clopidogrel. Patients with loss of function polymorphism in the *CYP2C19* gene are less responsive to clopidogrel [5,6], although the importance of this phenomenon remains controversial [7—10] and may be limited to the risk of stent thrombosis [11].

Proton-pump inhibitors (PPIs) are recommended in patients treated with dual antiplatelet therapy who are at high risk of gastrointestinal bleeding [12]. PPIs are metabolized primarily *via* the CYP2C19 and CYP3A4 isoenzymes [13] and are competitive inhibitors of CYP2C19 activity [14]. However, the contribution of the CYP2C19 isoenzyme to PPI biotransformation and *H. pylori* eradication rates [15] and the potency of inhibition of CYP2C19 activity [14] vary among different PPIs. CYP2C19 activity appears to affect the response to omeprazole, esomeprazole and lansoprazole [16—18] and to be inhibited by these PPIs [14,18]. This does not seem to be the case, at least not to the same extent, with pantoprazole [14,19] and rabeprazole [14,20].

Concerns about PPI and clopidogrel interaction were raised when omeprazole was found to inhibit the antiplatelet effect of clopidogrel in an *in vivo* study of 124 patients undergoing elective coronary stent implantation [21]. Several studies have suggested that omeprazole interacts with clopidogrel efficacy by inhibiting the formation of its active metabolite *via* CYP2C19 inhibition [22,23]. Whether this occurs with all PPIs or is even of significant amplitude with omeprazole remains a matter of debate [9,24—29]. However, it was recently demonstrated that generation of clopidogrel active metabolite and inhibition of platelet function are reduced less by the co-administration of dexlansoprazole or lansoprazole with clopidogrel than by the co-administration of esomeprazole or omeprazole [30].

As rabeprazole is a less potent CYP2C19 inhibitor than other PPIs [14], we performed a pharmacodynamic antiplatelet activity study of the interaction between standard recommended repeated doses of rabeprazole and clopidogrel in CYP2C19-genotyped healthy male subjects. Omeprazole and placebo were used as controls. Our primary objective was to demonstrate non-inferiority of rabeprazole over placebo using the change in platelet reactivity index (ΔPRI%) in good clopidogrel responders as derived from the vasodilator-stimulated phosphoprotein (VASP) assay as the primary endpoint.

Methods

Study design

This was a prospective, placebo- and active-controlled, open-label, blinded-evaluation, randomized, three-way crossover study. The study assessed the influence of rabeprazole (20 mg/day for 7 days) and omeprazole (20 mg/day for 7 days) on the antiplatelet effects and pharmacokinetics of clopidogrel (75 mg/day for 7 days) in 36 CYP2C19-genotyped non-smoking healthy Caucasian male subjects with normal basal platelet aggregation testing (> 50% aggregation to 1 μg/mL collagen, 1—2 mmol/L arachidonic acid and 10 μM adenosine diphosphate [ADP]), platelet count, complete blood count and prothrombin time. Subjects gave written informed consent to participate and to have CYP2C19 genotyping (but were not selected on the basis of their genotype) and the protocol was approved by the Committee for Protection of Human Subjects Île-de-France II and the French Medicine Agency.

Subjects were randomized based on a Latin square design to receive clopidogrel 75 mg/day in the morning in the fasting state for 7 days during three study periods separated by a drug-free period of 2—3 weeks, together with placebo, 20 mg of rabeprazole or 20 mg of omeprazole, given at the same time as clopidogrel. Platelet function evaluation (pharmacodynamics) was performed on day 1 before dosing (D1H0) and on day 7 before and 4 hours after the last intake of study drugs (D7H0 and D7H4, respectively). The pharmacokinetics of clopidogrel, its inactive carboxylic acid metabolite and the active metabolite were determined from blood samples taken before (H0) and at various times after administration of the last dose of clopidogrel with the concomitant drug (either placebo or PPI). Additional blood samples for determination of omeprazole, 5-hydroxyomeprazole, rabeprazole and rabeprazole thioether plasma concentrations were taken 3 and 4 hours postdose on day 7 to confirm proper exposure to PPIs.

Pharmacodynamic evaluations

The primary test to assess platelet function was based on the VASP phosphorylation level measured in whole blood using a flow cytometric assay (Platelet VASP®; Diagnostica Stago, Biocytex, Asnières, France) and a FACScan flow cytometer (Becton Dickinson, Le Pont de Claix, France). Results were expressed as platelet reactivity index (PRI%), calculated from the mean fluorescence intensity (MFI) of samples incubated with prostaglandin E1 (PGE1) alone or with both PGE1 and ADP simultaneously, using the following formula: $(MFI_{PGE1} - MFI_{PGE1+ADP}/MFI_{PGE1}) \times 100$, as previously described [3]. This test — also referred to as the VASP index — specifically assesses the activity of the P2Y12 receptor [31] (the target of clopidogrel antiplatelet action), and is widely used for monitoring the responsiveness to clopidogrel [32,33]. The percentage change in PRI on study day 7 just before the last administration of study drugs relative to baseline, i.e. prior to drug administrations (percentage change in ΔPRI [%] D7H0), was used as the primary study endpoint. ΔPRI (%) relative to day 1 was also calculated for D7H4.

Platelet aggregation was determined at the same time points as those used for VASP phosphorylation level

assessments, with ADP-induced platelet optical aggregometry (Biopool, Ventura, CA, USA; ADP 10 and 20 μM) using platelet-rich plasma adjusted to 250×10^9/L. Inhibition of platelet aggregation (IPA%) induced by ADP was calculated as: (MPA[day 1] − MPA[day 7]/MPA[day 1] × 100), where MPA is the maximal platelet aggregation induced by ADP. Platelet aggregation tests were performed on a TA-8 V optical platelet aggregometer (Soderel Medical, Heillecourt, France) within 3 hours of sampling in all subjects.

Pharmacodynamic evaluations were performed blind to the study period and the CYP2C19 genotype.

Pharmacokinetic evaluations

Blood samples for the clopidogrel assay were collected in 6 mL ethylenediaminetetraacetic acid (EDTA) vials stored at 4 °C, to which 38 μL of 2-bromo-3′-methoxyacetophenone (500 mM in acetonitrile) were added within 30 seconds of sampling to stabilize the active metabolite. Blood samples were centrifuged at 4 °C within 30 minutes and stored at −80 °C until assay. Clopidogrel, clopidogrel carboxylic acid, clopidogrel active metabolite, omeprazole, 5-hydroxyomeprazole, rabeprazole and rabeprazole thioether were extracted from plasma on a solid phase OASIS HLB cartridge (10 mg/1 mL; Waters SAS, Milford, MA, USA). Chromatographic separation and detection of all compounds was performed on a YMC—UltraHT Pro C18 analytical column (YMC, Dinslaken, Germany), using ultra-high-performance liquid chromatography coupled to a tandem mass spectrometry system (UPLC-Acquity-TQD; Waters SAS, Milford, MA, USA). Limits of quantification were 0.1 ng/mL for clopidogrel and clopidogrel active metabolite, 5 ng/mL for rabeprazole and rabeprazole thioether, 10 ng/mL for clopidogrel carboxylic acid and 50 ng/mL for omeprazole and 5-hydroxyomeprazole.

Pharmacokinetic variable values were calculated using WinNonlin® Professional, version 5.2 or higher (Pharsight Corp., Mountain View, CA, USA). The maximum plasma concentration (C_{max}) and the time of its occurrence (T_{max}) were obtained from observed values. The area under the concentration-time curve (AUC) in the sampled matrix during a dosing interval was calculated by linear up/log down trapezoidal summation. The apparent terminal rate constant (λz) after multiple dosing (1/hour), was determined by linear regression of the terminal points of the log-linear concentration-time curve. The apparent terminal half-life after multiple dosing (hours) was determined as (ln2/λz).

CYP2C19 genotyping and activity

The loss-of-function *CYP2C19* variants *2 (rs4244285) and *3 (rs4986893) were tested using polymerase chain reaction (PCR)-based specific probe hybridization and single base extension. 681G>A and 636G>A comprise the two common reduced functional variants *CYP2C19*2* and *CYP2C19*3*, respectively. Subjects with the *CYP2C19*1/*1* genotype were designated as CYP2C19 extensive metabolizer (EM) subjects.

The molar omeprazole/5-hydroxyomeprazole metabolic ratio in plasma samples at 3 hours was calculated as an index of CYP2C19 activity [34—36]. In one EM subject, this ratio was calculated from the blood sample taken at 4 hours because 5-hydroxyomeprazole was not detectable at 3 hours.

Statistical analyses

Sample size was calculated with the assumption that approximately 66% of subjects would be good antiplatelet responders, defined as subjects in whom the VASP index on study day 7 relative to study day 1 would decrease by ≥ 30%, with an expected intrasubject standard deviation of differences in ΔPRI of ≤ 14% [37] or a PRI value at day 7 below a cut-off value of 60%, as recently proposed for clopidogrel 75 mg daily maintenance dose [38]. With these assumptions, 36 subjects are sufficient to conclude non-inferiority of rabeprazole to placebo with 10% ΔPRI as the limit of non-inferiority with > 95% power when true difference in treatment means is equal to 2%. Pharmacodynamic analyses were first performed on good antiplatelet responders as defined above, then on all 36 subjects.

Mixed-effect models were fitted to the ΔPRI% data as the dependent variable, with sequence, treatment and period as factors and subject as a random effect. Ninety percent confidence intervals (CIs) were calculated for the difference in means between rabeprazole versus placebo. Non-inferiority was concluded if the upper limit of the 90% CI fell below 10%. This non-inferiority limit was chosen because it represents the difference between omeprazole and placebo reported by Gilard et al. [21] (10.7% in absolute value, 13.4% in relative value), which prompted the US Food and Drug Administration's warning on the interaction of PPIs with clopidogrel.

Additional post-hoc analyses were performed to compare the change in VASP index on study day 7 relative to study day 1 with omeprazole and rabeprazole relative to placebo, using the Wilcoxon signed-rank test in good antiplatelet responders. Post-hoc correlation analyses were performed using Pearson's correlation.

A linear mixed-effects model suitable for three-way crossover design was fitted to log-transformed pharmacokinetic variables, and 90% CIs for the ratio of the mean pharmacokinetic variables of clopidogrel were constructed using least-square means and intrasubject variance from the model. The above analysis was performed for clopidogrel active metabolite and clopidogrel major carboxylic acid metabolite. Bioequivalence was considered as demonstrated if the 90% CIs of the ratios for AUC_{0-24} and C_{max} between the placebo and PPI study periods fell in the range 80—125%.

Results

Thirty-six subjects completed the three study periods. Mean age, body weight and body mass index were 33.6 ± 7.9 years, 74.1 ± 8.7 kg and 23.6 ± 2.3 kg/m², respectively. Of these 36 subjects, 23 were *CYP2C19*1/*1* EMs, 12 were heterozygous *CYP2C19*1/*2* and one was a poor metabolizer with the *CYP2C19*2/*2* genotype.

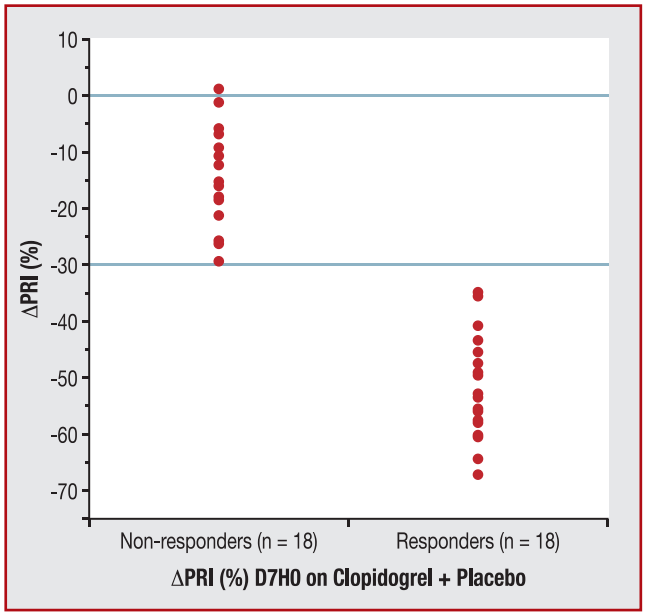

Figure 1. Change in vasodilator-stimulated phosphoprotein (VASP) platelet reactivity index (PRI) at trough on day 7 of clopidogrel 75 mg/day in the presence of placebo in 36 healthy subjects. Subjects in whom the VASP index on day 7 relative to day 1 was decreased by ≥ 30% were defined as good antiplatelet responders.

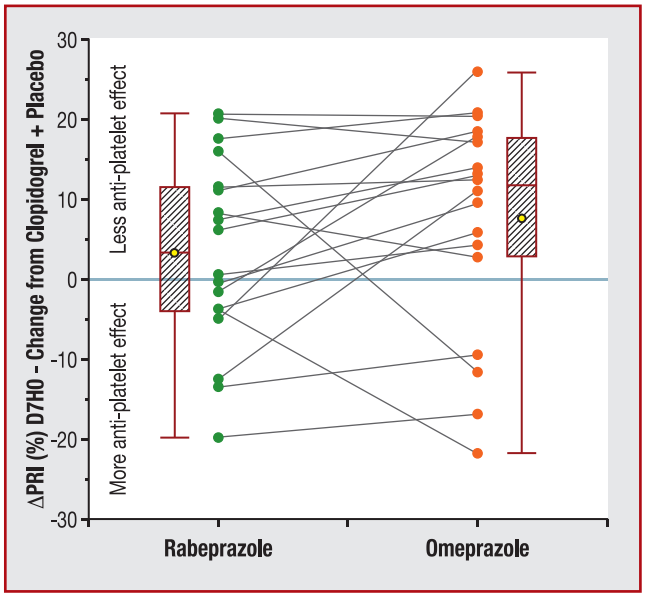

Figure 2. Change in vasodilator-stimulated phosphoprotein platelet reactivity index (PRI) at trough on day 7 of clopidogrel 75 mg/day during co-administration of rabeprazole and omeprazole in 18 good antiplatelet responders. Each box plot represents the interquartile range with mean (horizontal line in the box) and median (dot in the box); the whiskers represent the 5–95 percentiles. $P = 0.067$.

Platelet function assays

Baseline VASP index before administration of clopidogrel was not significantly different across study periods ($P = 0.60$). As expected, there was considerable interindividual variability in platelet function inhibition, as measured by use of the VASP index (VASP ΔPRI%) on day 7 of the clopidogrel plus placebo study period prior to last drug administration (D7H0) (Fig. 1). The decrease in VASP index was < 30% in 18 subjects while the other 18 subjects were classified as good clopidogrel responders (change of VASP index ≥ 30%). Table 1 shows the results of platelet aggregation studies on day 7 (D7) of each study period before (H0) and 4 hours after (H4) administration of the last dose of clopidogrel together with placebo, omeprazole and rabeprazole.

In good clopidogrel responders (as evaluated by VASP assay), the upper limit of the 90% CI non-inferiority threshold of 10% was crossed during co-prescription of omeprazole but not during co-prescription of rabeprazole at D7H0 and D7H4. Therefore, in this predefined group of subjects in whom significant antiplatelet activity was present during administration of clopidogrel with placebo, the antiplatelet effect of clopidogrel during co-administration of rabeprazole was non-inferior to placebo, whereas this was not the case during omeprazole co-administration. In this group, the increase in VASP reactivity index relative to placebo did not differ significantly during rabeprazole and omeprazole co-administration ($P = 0.067$; Fig. 2). However, the change in VASP index from placebo was statistically significant during omeprazole ($P = 0.017$) but not rabeprazole ($P = 0.26$) co-administration at D7H0 and D7H4 ($P < 0.009$ and $P = 0.20$, respectively) (Table 1)

When considering the entire population of 36 subjects, the VASP index at D7H0 and D7H4 was not significantly altered by co-administration of omeprazole or rabeprazole. The increase of VASP index at D7H4 with omeprazole did not reach statistical significance ($P = 0.056$). Between-period differences were less consistent when considering inhibition of platelet aggregation (IPA%) induced by ADP (Table 1). The 10% non-inferiority threshold was crossed in all subjects for both omeprazole and rabeprazole only in the presence of ADP 10 μM.

CYP2C19 genotype influenced the antiplatelet effects of clopidogrel. Compared with subjects with the *CYP2C19*1/*2* genotype ($n = 12$), EM subjects ($n = 23$) had more antiplatelet effects, as assessed by the change in VASP index at D7H0 during placebo co-administration ($-39.3 \pm 0.20\%$ in *CYP2C19*1/*1 vs.* $-22 \pm 0.15\%$ in *CYP2C19*1/*2*; $P < 0.015$). Among the 23 EM subjects, 15 were good antiplatelet responders. One subject became a non-responder with omeprazole; none became non-responders with rabeprazole (Fig. 3). Among the 12 subjects with the *CYP2C19*1/*2* genotype, only three were good antiplatelet responders during administration of clopidogrel with placebo. One subject became a non-responder with both rabeprazole and omeprazole (Fig. 3).

Clopidogrel disposition kinetics

Table 2 shows the main pharmacokinetic variables for clopidogrel active metabolite in all subjects. We also analysed pharmacokinetics variables in EM subjects homozygous for *CYP2C19*1*1*. Fig. 4 shows the plasma concentration *versus* time profile of clopidogrel active metabolite in all subjects.

In the entire population, despite a significant fall compared with placebo, the AUC_{0-24} of clopidogrel active metabolite during rabeprazole co-administration remained

Table 1 Antiplatelet effects of clopidogrel 75 mg/day for 7 days in the presence of placebo, omeprazole and rabeprazole.

	Treatment	*n*	Least square		Pairwise comparisons			
			Mean (%)	95% CI	Pair	Difference (%)	90% CI	*P*[a]
VASP ΔPRI (%)								
Good VASP antiplatelet responders[b]								
Day 7/hour 0	RABE	18	−47.3	(−52.5; −42.1)	RABE/OME	−4.1	(−9.2; 1.0)	0.18
					RABE/PLBO	3.4	(−1.7; 8.5)	0.26
	OME	18	−43.2	(−48.4; −38.0)	OME/PLBO	7.5	(2.5; 12.6)	0.017
	PBO	18	−50.7	(−55.9; −45.6)				
Day 7/hour 4	RABE	18	−56.2	(−62.5; −49.9)	RABE/OME	−4.9	(−10.5; −0.8)	0.15
					RABE/PLBO	4.4	(−1.2; 9.9)	0.2
	OME	18	−51.3	(−57.6; −45.1)	OME/PLBO	9.2	(3.6; 14.8)	0.0087
	PBO	18	−60.3	(−66.8; −54.3)				
All subjects								
Day 7/hour 0	RABE	36	−32.1	(−38.8; −25.5)	RABE/OME	−1.6	(−5.1; 1.8)	0.44
					RABE/PLBO	0.4	(−3.1; 3.8)	0.85
	OME	36	−30.5	(−37.5; −23.9)	OME/PLBO	2	(−1.5; 5.5)	0.34
	PBO	36	−32.5	(−39.2; −25.9)				
Day 7/hour 4	RABE	36	−39.8	(−47.4; −32.1)	RABE/OME	−3.7	(−7.2; −0.1)	0.089
					RABE/PLBO	0.5	(−3.1; 4.0)	0.82
	OME	36	−36.1	(−43.8; −28.5)	OME/PLBO	4.2	(0.6; 7.7)	0.056
	PBO	36	−40.3	(−47.9; −32.6)				
Inhibition of platelet aggregation induced by ADP day 7/hour 0								
All subjects								
ADP 20 μM	RABE	36	39.4	(32.4; 46.4)	RABE/OME	4.3	(−0.1; 8.8)	0.11
					RABE/PLBO	−0.8	(-5.3; 3.7)	0.77
	OME	36	35.1	(28.1; 42.1)	OME/PLBO	−5.1	(−9.6; −0.6)	0.063
	PBO	35	40.2	(33.1; 47.2)				
ADP 10 μM	RABE	36	39.8	(32.7; 46.9)	RABE/OME	0.6	(−4.7; 5.8)	0.86
					RABE/PLBO	−6.3	(−11.6; −1.1)	< 0.05
	OME	36	39.2	(32.1; 46.3)	OME/PLBO	−6.9	(−12.2; −1.6)	0.033
	PBO	35	46.1	(39.0; 53.3)				

ADP: adenosine diphosphate; CI: confidence interval; IPA: inhibition of platelet aggregation; OME: omeprazole; PLBO: placebo; ΔPRI: change in platelet reactivity index; RABE: rabeprazole; VASP: vasodilator-stimulated phosphoprotein.

[a] *P* values for equality of means.

[b] Good antiplatelet responders were defined as subjects in whom the VASP index on day 7 relative to day 1 was decreased by ≥ 30%.

Table 2 Pharmacokinetics of clopidogrel active metabolite on day 7 of clopidogrel 75 mg/day in the presence of placebo, omeprazole and rabeprazole.

	Treatment	*n*	Geometric least square		Pairwise comparisons			
			Mean	95% CI	Pair	Ratio (%)	90% CI	*P*
All subjects								
AUC_{0-24} (ng*hours/mL)	RABE	36	26.6	(23.1; 30.6)	RABE/OME	108.1	(100.0; 116.9)	0.10
					RABE/PLBO	88.4	(81.7; 95.6)	0.01
	OME	36	24.6	(21.4; 28.3)	OME/PLBO	81.7	(75.6; 88.4)	< 0.0001
	PLBO	36	30.1	(26.2; 34.6)				
C_{max} (ng/mL)	RABE	36	15.1	(12.5; 18.1)	RABE/OME	105.8	(90.6; 123.6)	0.54
					RABE/PLBO	72.1	(61.7; 84.2)	< 0.001
	OME	36	14.3	(11.9; 17.1)	OME/PLBO	68.1	(58.3; 79.5)	0.0001
	PLBO	36	20.9	(17.4; 25.2)				
$t_{1/2}$ (hours)	RABE	19	4.5	(2.7; 7.7)	RABE/OME	91.5	(56.8; 147.4)	0.75
					RABE/PLBO	105.3	(65.3; 169.5)	0.86
	OME	19	5.0	(2.9; 8.4)	OME/PLBO	115.0	(71.4; 185.3)	0.62
	PLBO	19	4.3	(2.6; 7.3)				
CYP2C19 *1/*1								
AUC_{0-24} (ng*hours/mL)	RABE	23	29.8	(25.7; 34.5)	RABE/OME	107.1	(97.8; 117.3)	0.21
					RABE/PLBO	82.3	(75.1; 90.2)	0.0009
	OME	23	27.8	(24.0; 32.2)	OME/PLBO	76.8	(70.1; 84.2)	< 0.0001
	PLBO	23	36.2	(31.3; 41.9)				
C_{max} (ng/mL)	RABE	23	16.7	(13.3; 21.1)	RABE/OME	104.1	(86.6; 125.3)	0.72
					RABE/PLBO	66.8	(55.4; 80.5)	0.0008
	OME	23	16.1	(12.8; 20.3)	OME/PLBO	64.1	(53.3; 77.2)	0.0002
	PLBO	23	25.1	(19.9; 31.6)				
$t_{1/2}$ (hours)	RABE	10	6.4	(3.3; 12.6)	RABE/OME	126.5	(62.5; 256.1)	0.57
					RABE/PLBO	75.8	(37.0; 155.4)	0.51
	OME	10	5.1	(2.5; 10.1)	OME/PLBO	59.9	(28.1; 127.5)	0.25
	PLBO	10	8.5	(4.2; 17.0)				

AUC_{0-24}: area under plasma concentration-time curve from 0 to 24 hours; CI: confidence interval; C_{max}: maximum observed plasma concentration; $t_{1/2}$: apparent elimination half-life; OME: omeprazole; PLBO: placebo; RABE: rabeprazole.

within the bioequivalence limits relative to the placebo study period. This was not the case during omeprazole co-administration. Bioequivalence was not met for C_{max} during administration of both PPIs. In EM subjects, bioequivalence was not met for any of the measured variables during both omeprazole and rabeprazole co-administration. Mean T_{max} was 0.67 hours in the three study groups.

The AUC_{0-24} and apparent elimination half-life of clopidogrel and its main carboxylic acid metabolite remained within the bioequivalence range during both omeprazole and rabeprazole co-administration (data not shown). Other variables that were not bioequivalent were: C_{max} of clopidogrel during the rabeprazole study period (ratio of 85.1, 90% CI 75.1—98.0); and C_{max} of carboxylic acid metabolite during rabeprazole (ratio of 82.0, 90% CI 72.2—93.2) and omeprazole (ratio of 83.3, 90% CI: 73.3—94.6) co-administration.

In the 23 subjects who were CYP2C19 EMs, AUC_{0-24} of clopidogrel active metabolite decreased significantly during co-administration of omeprazole and rabeprazole (Fig. 5).

Regression analyses

Platelet reactivity (VASP PRI) at D7H0 correlated negatively with clopidogrel active metabolite AUC_{0-24} during placebo ($r^2 = 0.32$; $n = 36$; $P < 0.001$), rabeprazole ($r^2 = 0.30$; $n = 36$; $P < 0.001$) and omeprazole ($r^2 = 0.18$; $n = 36$; $P < 0.007$) co-administration. The change in VASP ΔPRI at D7H0 from placebo during each PPI study period correlated positively with the change in clopidogrel active metabolite AUC_{0-24} during co-administration of the corresponding drug: rabeprazole ($r^2 = 0.11$; $n = 36$; $P < 0.025$) or omeprazole ($r^2 = 0.11$; $n = 36$; $P < 0.027$).

The omeprazole metabolic ratio could not be determined in one EM subject. The change in platelet inhibition (VASP ΔPRI) at D7H0 during the placebo period and the change in platelet aggregation (IPA%) induced by ADP 10 μM (but not 20 μM) at D7H0 correlated positively with the omeprazole metabolic ratio ($r^2 = 0.19$; $n = 35$; $P < 0.006$ and $r^2 = 0.17$; $n = 35$; $P < 0.009$, respectively), a higher metabolic ratio (i.e. less CYP2C19 activity) being associated with less antiplatelet effect. No significant correlation was found between the change in VASP index or the change in the AUC for clopidogrel active metabolite during omeprazole or rabeprazole periods and CYP2C19 activity as assessed by use of the omeprazole metabolic ratio.

There was no correlation between omeprazole plasma concentration at 3 hours (mean ± standard deviation: 665 ± 576 ng/mL), or rabeprazole (351 ± 233 ng/mL) or

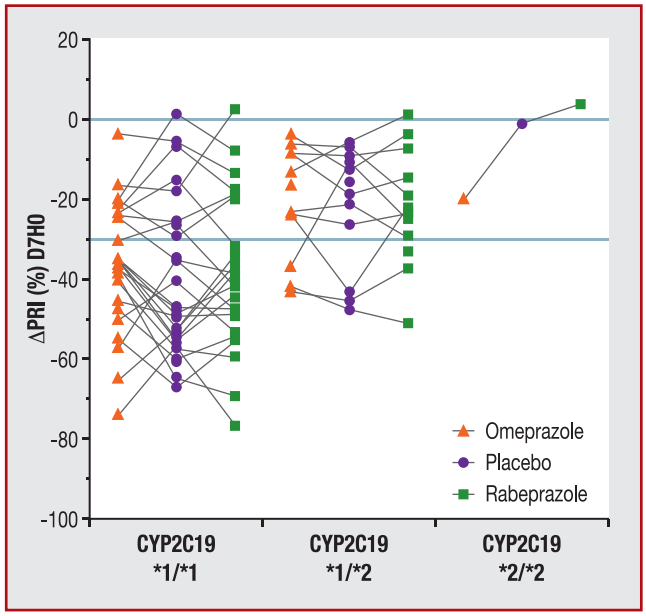

Figure 3. Change in vasodilator-stimulated phosphoprotein platelet reactivity index (PRI) at trough on day 7 of clopidogrel 75 mg/day in the presence of placebo, rabeprazole and omeprazole in 36 healthy subjects, according to CYP2C19 genotypes. CYP: cytochrome P450.

rabeprazole thioether (129 ± 85 ng/mL) plasma concentration at 4 hours, and the change in VASP ΔPRI during the corresponding PPI combination therapy.

The falls in clopidogrel active metabolite C_{max} and AUC_{0-24} during rabeprazole and omeprazole co-administration were correlated ($r^2 = 0.56$; $n = 36$; $P < 0.001$ in both cases) and the slopes of these relationships did not differ significantly from unity.

Discussion

This randomized crossover study was designed to analyse the potential interaction between clopidogrel and rabeprazole, omeprazole being used as a putative positive control. It was conducted in healthy male volunteers, thus eliminating potential confounding factors, including smoking, non-compliance and other medications.

As an inhibitory interaction is not expected to occur in subjects who do not have an adequate response in the absence of inhibitor, the predefined group of VASP good antiplatelet responders was chosen to examine the pharmacodynamic interactions between rabeprazole and clopidogrel. The VASP index is considered as a specific test for evaluating P2Y12 inhibition, while light-transmission aggregometry is used to predict outcome during dual

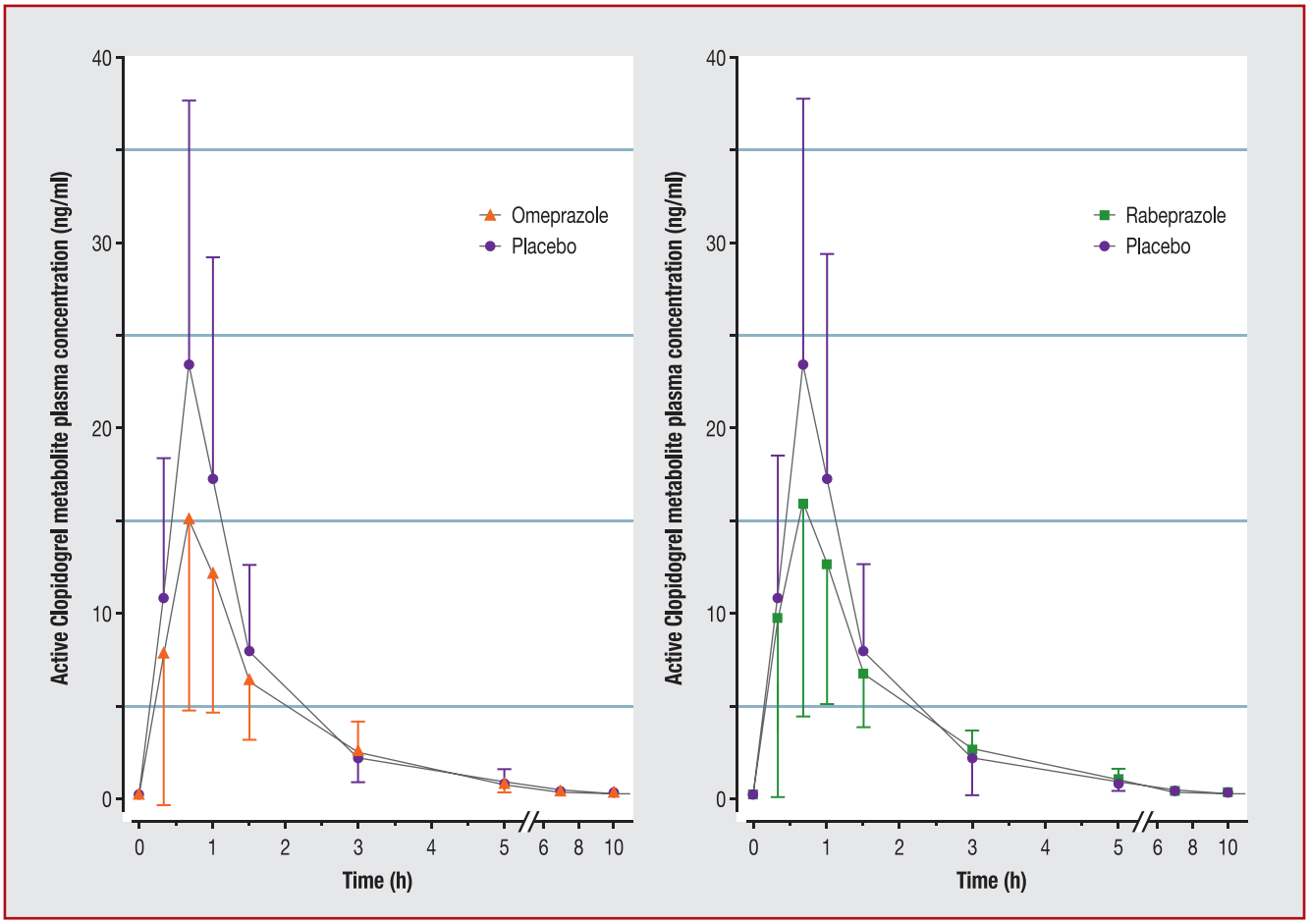

Figure 4. Mean (standard deviation) plasma concentration of clopidogrel active metabolite as a function of time on day 7 of clopidogrel 75 mg/day in the presence of placebo, rabeprazole and omeprazole in 36 healthy subjects.

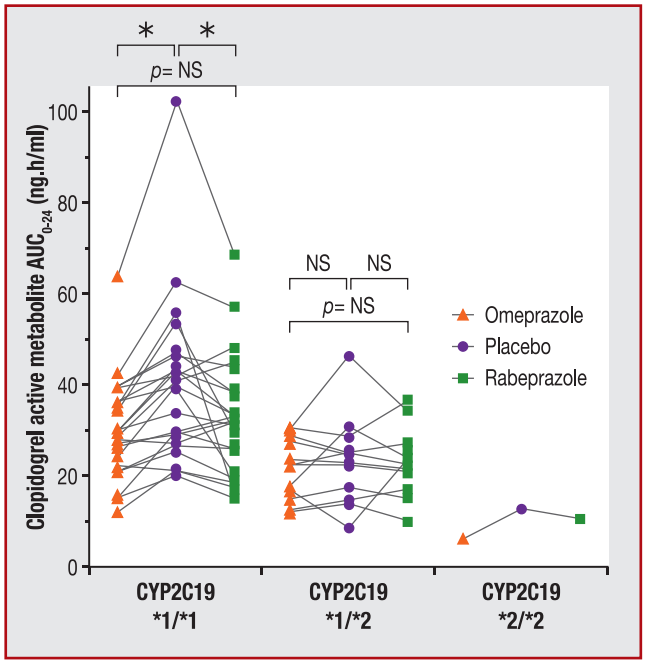

Figure 5. Area under the plasma concentration-time curve from 0 to 24 hours for clopidogrel active metabolite on day 7 of clopidogrel 75 mg/day in the presence of placebo, rabeprazole and omeprazole in 36 healthy subjects, according to CYP2C19 genotypes. CYP: cytochrome P450; NS: not significant. * $P < 0.001$.

antiplatelet therapy, although both tests have a predictive value [31,33,39,40]. In the group of good VASP antiplatelet responders, the clopidogrel antiplatelet effect remained non-inferior to placebo at D7H0 and D7H4 during rabeprazole co-administration, whereas it crossed the limit of non-inferiority during omeprazole co-administration. Therefore, from a pharmacodynamic point of view, in subjects in whom clopidogrel elicits a marked antiplatelet effect, inhibition of clopidogrel antiplatelet action is minimal with rabeprazole, whereas a statistically significant reversal of clopidogrel effects is observed with omeprazole.

However, when using aggregometry — a test less specific for P2Y12 but that reflects the global platelet function — inhibition of platelet aggregation induced by ADP 10 μM significantly decreased with both omeprazole and rabeprazole in the entire population. These results are in line with pharmacokinetic analysis, showing a decreased exposure to clopidogrel active metabolite with both PPIs. The AUC_{0-24} and C_{max} of clopidogrel active metabolite significantly decreased with both omeprazole and rabeprazole, and conditions of bioequivalence were not met, except for AUC_{0-24} with rabeprazole. This discrepancy between pharmacokinetic and pharmacodynamic variable (VASP) changes was also found in a drug interaction study that examined the influence of pantoprazole (80 mg/day) on clopidogrel antiplatelet effects and exposure to its active metabolite [19]. In this study, no significant change in VASP index (but significant changes in ADP 5 μM-induced maximum platelet aggregation) was found despite a statistically significant decrease in clopidogrel active metabolite AUC_{0-24} and C_{max} with pantoprazole, of the same order of magnitude as that found in our study. Greater decreases in exposure to clopidogrel active metabolite were found with high-dose omeprazole (80 mg/day) in a study by Angiollilo et al. [19] and were associated with significant inhibition of VASP and ADP-induced platelet aggregation. In our study, the change in VASP index with PPIs was weakly associated ($r^2 = 0.11$) with the change in exposure to clopidogrel active metabolite produced by omeprazole and rabeprazole, although the association between VASP index and clopidogrel active metabolite AUC_{0-24} was stronger ($r^2 = 0.32$) during administration of clopidogrel with placebo. Taken together, these results suggest that a certain extent of pharmacokinetic interaction with clopidogrel active metabolite is necessary to produce a significant pharmacodynamic interaction; this could explain why the amplitude of the pharmacodynamic interaction we found with omeprazole was limited in size.

As expected [22,23], CYP2C19 genotype and activity influenced clopidogrel antiplatelet activity in the absence of PPI, with greater inhibition of platelet aggregation in homozygous EM subjects compared with subjects with at least one non-functional *CYP2C19* allele. Also, during the placebo study period, clopidogrel-induced change in VASP index and platelet aggregation induced by 10 μM (but not 20 μM) ADP correlated with CYP2C19 activity, as assessed by the use of the omeprazole metabolic ratio. However, the association was weak, with only about 18% of antiplatelet effect explained by the omeprazole metabolic ratio. During PPI administrations, no significant correlation was found between the change in VASP index or the change in the AUC of clopidogrel active metabolite and CYP2C19 activity as assessed by the omeprazole metabolic ratio. Such an absence of association by regression analysis raises the question of the role of CYP2C19 inhibition in explaining our findings. Rabeprazole is mainly metabolized by non-enzymatic reduction to rabeprazole thioether [41] and is a less potent inhibitor of CYP2C19 than omeprazole [14,42,43]. This may explain why rabeprazole had less effect than omeprazole on the clopidogrel-induced change in VASP index, although the study was not powered to test the statistical significance of this difference. However, this does not explain the similarity of the pharmacokinetic interaction of clopidogrel active metabolite with both PPIs. In this respect, pantoprazole [19] and rabeprazole appear to have similar profiles. Also, rabeprazole thioether, the main circulating metabolite of rabeprazole, is a CYP2C19 inhibitor [14] and could have contributed to the observed effects. Finally, CYP2C19 is not the only CYP that contributes to the bioactivation of clopidogrel to its active metabolite [4]. CYP2C19 contributes to the first step of clopidogrel metabolism to its 2-oxo unstable metabolite by 45% while CYP1A2 and CYP2B6 contribute by 36% and 19%, respectively. CYP2C19 contributes to the final step of clopidogrel active metabolite formation from 2-oxoclopidogrel by only 20% while CYP3A4, CYP2B6 and CYP2C9 contribute by 40%, 33% and 7%, respectively [4]. It is therefore conceivable that non-CYP2C19-mediated mechanisms may contribute to the interaction between PPIs and clopidogrel.

For uniformity, our study included only young male volunteers, a population that does not reflect the diversity of patients with ischaemic heart disease who usually receive dual antiplatelet therapy and an initial loading dose of clopidogrel. In the target population, clopidogrel is usually prescribed with aspirin, and it has been suggested that

inhibition of antiplatelet effect may result from an interaction of PPIs with aspirin absorption [44,45], independent of the interaction with clopidogrel [46,47]. Inhibition of clopidogrel absorption by PPIs is unlikely to occur because clopidogrel is a weak base that is not absorbed from the stomach, unlike aspirin. To our knowledge, only one study has compared the effects of omeprazole and rabeprazole on the antiplatelet action of clopidogrel in patients on dual antiplatelet therapy [48]. In this open-label study in a limited number of patients, both omeprazole and rabeprazole reduced the effects of clopidogrel on platelet aggregation induced by 10 μM ADP. However, the authors acknowledged that their study was not placebo controlled and did not have the power to detect a difference between omeprazole and rabeprazole. Another recent study reported on the interaction between a single 300 mg dose of clopidogrel and rabeprazole (20 mg) and did not find an interaction [49].

Conclusions

Our study, despite the limitations indicated above, suggests that the interaction between rabeprazole and clopidogrel is likely to be less pronounced than the interaction between omeprazole and clopidogrel in patients with heart disease. The study also shows that the interaction with omeprazole is of small amplitude when the standard therapeutic dose of 20 mg/day is used. Under our experimental conditions and PPIs doses, there was no significant pharmacodynamic interaction between rabeprazole or omeprazole and clopidogrel, despite a significant decrease in the formation of clopidogrel active metabolite; this is consistent with a previous study with pantoprazole [19] and suggests that there is a threshold of decreased clopidogrel active metabolite formation that is required to produce a pharmacodynamic interaction.

Disclosure of interest

C. Funck-Brentano has received consulting and lecture fees and an institutional grant from Janssen-Cilag for his participation in this study; he has also received consulting fees from BMS, sanofi-aventis and Tibotec, independent of this study. J. Szymezak, O. Steichen, D. Ducint, M. Molimard and V. Remones have declared no conflict of interest. M. Azizi has received consulting and lecture fees from Novartis, Sanofi and Actelion, independent of this study. P. Gaussem has received grant support from Janssen-Cilag for her participation in this study.

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