

Does the Timing of PPI Dosing Influence the Antiplatelet Effect of Clopidogrel? Results of the SPACING Study

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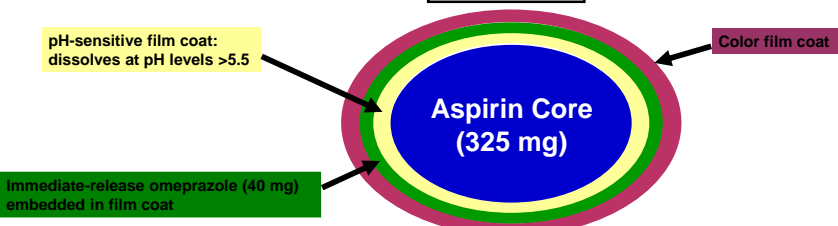
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INTRODUCTION

- Clopidogrel + aspirin (DAPT) reduces ischemic event occurrence in stented patients.¹
- Co-administration of proton pump inhibitors (PPIs) with DAPT reduces gastrointestinal bleeding and was recommended in the 2008 ACCF/ACG/AHA expert consensus document.¹
- New evidence of a decreased pharmacodynamic (PD) effect and an increased occurrence of ischemic events with PPI + clopidogrel [mostly delayed release (DR) omeprazole] was highlighted by a Food and Drug Administration advisory and a European Medicines Agency public statement prompting an update in the 2010 ACCF/ACG/AHA expert consensus document.^{2,3}
- Spacing of DR omeprazole and clopidogrel did not lessen the PD interaction.⁴
- PA325240 is a novel agent that combines 325 mg enteric-coated aspirin (EC-ASA) + 40mg immediate-release (IR) omeprazole.⁵
- PA32520 has been associated with fewer gastroduodenal ulcers than EC-ASA 81 mg qd or EC-ASA 325 mg qd after 4 weeks of therapy.⁵
- Given the significantly different pharmacokinetic profile of IR omeprazole, the SPACING study was conducted to determine if spaced PA32540 + clopidogrel reduces PD interaction.

1. Bhatt DL et al. *Circulation* 2008;118:1894-909.
2. Gurbel PA et al. *Drug, Healthcare and Safety*. 2010 (in press).
3. Abraham NS et al. *J Am Coll Cardiol* 2010; DOI:10.1016/j.jacc.2010.09.010
4. Ferreira JL et al. *Circ Cardiovasc Interv*. 2010;3:436-41.
5. Gurbel PA et al. Presented at International Society for Thrombosis and Haemostasis Meeting, Boston, MA, USA, 2009; abstract # 3120.

PA32540



OBJECTIVE

- To evaluate whether platelet inhibition during dual antiplatelet therapy with PA32540 + clopidogrel administered synchronously or spaced 10 h apart is non-inferior to a strategy of synchronous administration of 325 mg enteric coated aspirin + clopidogrel.

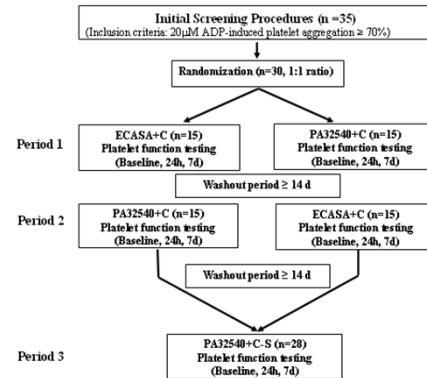
METHODS

Subjects and Sample Collection

- Randomized, open-label, single-center, crossover study in healthy volunteers ≥ 40 y.o.
- Pre-treatment blood samples collected after overnight fast (≥10 h) and before morning dosing.
- 24 h and 7 d blood samples collected after overnight fast and 1 h post-clopidogrel administration.
- 3.2% trisodium citrate (Vacutainer) used for light transmittance aggregometry (LTA) and vasodilator-stimulated phosphoprotein phosphorylation (VASP-P) assay.
- 3.2% sodium citrate (Greiner Bio-One Vacuette® North America, Inc. Monroe, NC) used for VerifyNow.

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Study Design



ECASA+C:

- d1: EC aspirin 325mg (Ecotrin®) + clopidogrel 300mg
- d2-7: EC aspirin 325mg + clopidogrel 75mg

PA32540+C:

- d1: one tablet of PA32540 + clopidogrel 300mg
- d2-7: one tablet of PA32540 + clopidogrel 75mg

PA32540+C-S:

- d1: one tablet of PA32540 + clopidogrel 300 mg 10 h later
- d2-7: one tablet of PA32540 + clopidogrel 75 mg 10 h later

Platelet Function Testing and Statistical Analysis

Light Transmittance Aggregometry (LTA, Chronolog, Inc.)

- Platelet aggregation (PA) (5 and 20 μM ADP, maximal) measured in platelet rich plasma using platelet poor plasma as a reference.

VerifyNow™ P2Y12 and Aspirin Assays (Accumetrics, Inc.)

- The VerifyNow™ System measures ADP + prostaglandin (PG) E₁ and arachidonic acid -simulated platelet aggregation to fibrinogen-coated beads and the change in optical signal is reported as P2Y12 Reaction Units (PRU) and Aspirin reaction units (ARU), respectively.

Vasodilator Stimulated Phosphoprotein-Phosphorylation (VASP-P) Assay (Biocytex)

- VASP-P levels were determined in whole blood by measuring mean fluorescence intensity (MFI) in PGE₁ and PGE₁+ADP stimulated blood samples and Platelet Reactivity Index (VASP-PRI) was calculated according to the formula: PRI = [(MFI(PGE₁) - MFI(PGE₁+ADP)) / MFI(PGE₁)] x 100%.

Statistical Analysis

- Primary endpoint:

Relative inhibition of PA at d7 defined as: (IPA) (%) = [(PA₀ - PA₇) / PA₀] x 100%; (PA₇ = maximum 20μM ADP-induced PA at d7; PA₀ = maximum 20μM ADP-induced PA at baseline).

- Primary Analysis:

Non-inferiority of PA32540 compared to ECASA defined by upper bound of the 95% confidence interval for difference in least squared means of IPA between treatments ≤ 10%.

- Analyses performed using SPSS version 13 (SPSS Inc., Chicago, Ill.); p ≤ 0.05 was statistically significant.

RESULTS

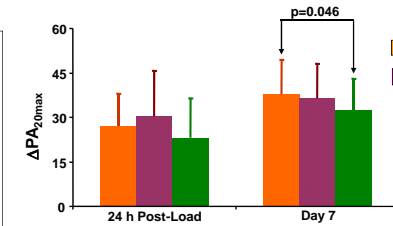
Demographics

- Healthy Caucasian (n=29); African American (n=1); Asian volunteers (n=2); mean age=45y; BMI =26 kg/m².
- n=30 completed the first 2 periods, n = 28 completed the final period.
- No SAE's and no subject withdrawal from study due to AE's. AE's similar between treatments.

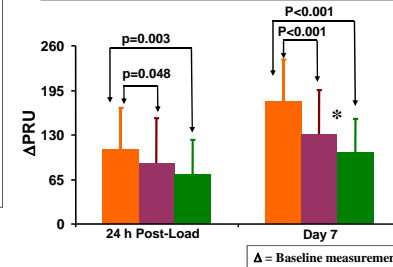
Inhibition of Platelet Function Synchronous Administration

Endpoint (Mean)	ECASA25+C (n=30)	PA32540+C (n=30)	Diff. in LSM (95% CI) ¹
At 24 h Post-Loading			
2mM AA-PA	91.8	91.5	0.3 (-0.6, 1.2)
ARU	34.0	34.5	-0.5 (-2.7, 1.7)
20μM ADP-PA	31.2	26.1	5.1 (0.3, 10.0)
5μM ADP-PA	41.4	36.7	4.7 (-1.2, 10.7)
VASP-PRI	23.0	17.8	5.2 (-0.1, 10.3)
PRU	33.3	23.4	9.9 (4.0, 15.9)
At d 7			
2mM AA-PA	91.2	91.4	-0.3 (-0.9, 0.4)
ARU	34.5	36.4	-1.9 (-6.0, 2.1)
20μM ADP-PA ²	44.0	36.7	7.3 (1.4, 13.2)
5μM ADP-PA	54.0	45.9	8.1 (2.5, 13.7)
VASP-PRI	52.8	34.5	18.3 (10.7, 26.0)
PRU	56.1	32.8	23.4 (17.9, 28.8)

ΔPA_{20max} by Time and Treatment



ΔPRU by Time and Treatment



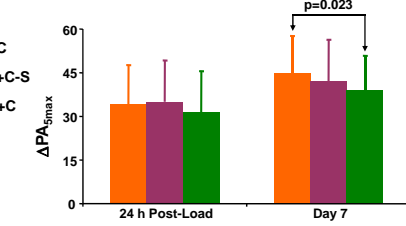
Inhibition of Platelet Function Spaced Administration

Endpoint (Mean)	ECASA325+C (n=28)	PA32540+C-S (n=28)	Diff. in LSM (95% CI) ¹
At 24 h Post-Loading			
20 μM ADP-PA	31.8	33.2	-1.4 (-7.5, 4.8)
5 μM ADP-PA	42.0	38.7	3.3 (-4.5, 11.1)
VASP-PRI	23.3	26.7	-3.4 (-8.6, 1.7)
PRU	33.9	27.1	6.8 (0.6, 13.0)
At d 7			
20 μM ADP-PA ²	44.4	40.0	4.4 (-0.8, 9.6)
5 μM ADP-PA	54.1	46.6	7.5 (0.9, 14.1)
VASP-PRI	51.9	41.7	10.1 (3.6, 16.7)
PRU	56.5	40.6	15.9 (9.9, 21.8)

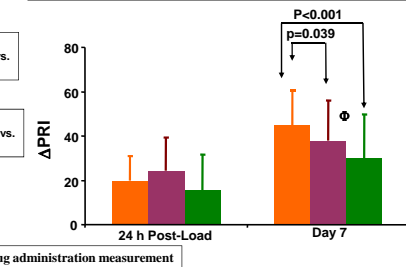
(Primary Analysis)

- 1= Negative values represent increase in inhibition.
- 2= Primary endpoint.

ΔPA_{5max} by Time and Treatment



ΔPRI by Time and Treatment



- This first evaluation suggests that administration of IR omeprazole (contained in PA32540) + clopidogrel may be associated with a different PD profile than DR omeprazole + clopidogrel.
- In our study: 1) PD effect of spacing PA32540 + clopidogrel was non-inferior to clopidogrel + ECASA measured by aggregometry.
- 2) Spacing numerically lessened the interaction observed with synchronous administration.
- Further investigations of PA32540 are indicated in patients requiring DAPT and omeprazole therapy.