Oral Dosing of PRT060128, a Novel Direct-acting, Reversible P2Y12 Antagonist Overcomes High Platelet Reactivity in Patients Non-responsive to Clopidogrel Therapy

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Introduction

- Prasugrel: better clinical outcomes vs. clopidogrel but still a ~10% recurrent ischemic event rate and greater bleeding. [1]
- Irreversible platelet inhibition by thienopyridines is a major limitation in patients needing surgery.
- A new reversible, direct acting $P2Y_{12}$ receptor inhibitor, PRT060128 (Portola Pharmaceuticals Inc, South San Francisco, CA) has both oral and parenteral formulations.

1. Wiviott SD et al. *N Engl J Med*. 2007;357:2001-15.

Objective

- Determine the antiplatelet effect of a single, oral 60 mg dose of PRT060128 administered to stented patients screened for high platelet reactivity (HPR) to ADP during standard dose clopidogrel and aspirin therapy.

Methods- Patients

- Stable CAD (n=50) on chronic daily 75mg clopidogrel + 81mg aspirin
- 20 patients (5 pts. previously identified with HPR at our center) had HPR
- HPR: ≥43% 5μM ADP-induced platelet aggregation:
  upper tertile of pre-stenting platelet aggregation in patients on C + A associated with an increased risk of 6 mo post-stenting ischemic events (Bliden KP et al. *J Am Coll Cardiol.* 2007;49:657-66).
- 7-14 d post-screening visit:
  60mg p.o. PRT060128 at 12-16 h after the previous day's dose of C.
- Continued C + A
- F/U visits at 24 h and 7-10d post-dosing.

Methods

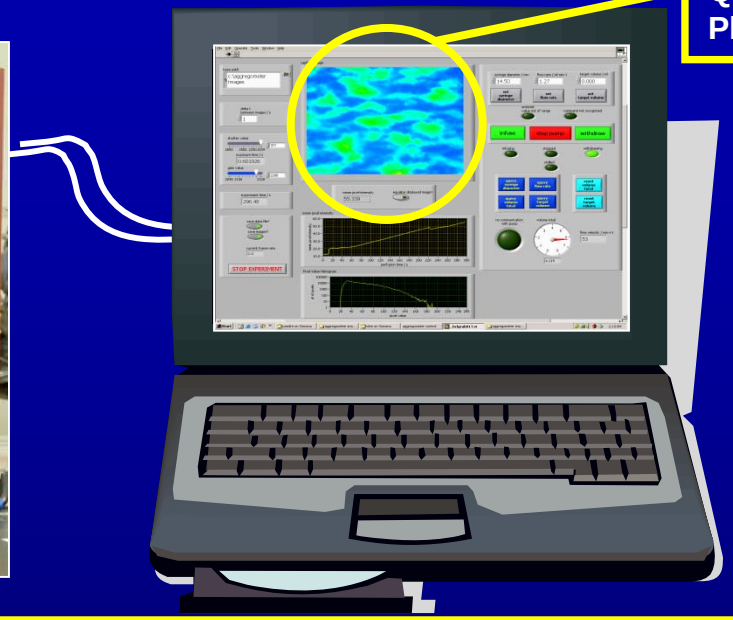
Timing of Blood Samples

- Pre-dose, and at 4, 6, and 24h and 7-10 d post-dosing

Platelet Function Measurements

- 5 and 20 μM ADP- induced platelet aggregation (citrate)
- 10 μM ADP- induced platelet aggregation (Xa inhibitor, C921-78)
- Thrombelastography (TEG)
- VerifyNow P2Y12 assay
- Vasodilator-stimulated phosphoprotein (VASP)
- Perfusion chamber assay (Xa inhibitor, C921-78)

Perfusion Chamber Assay (PCA)

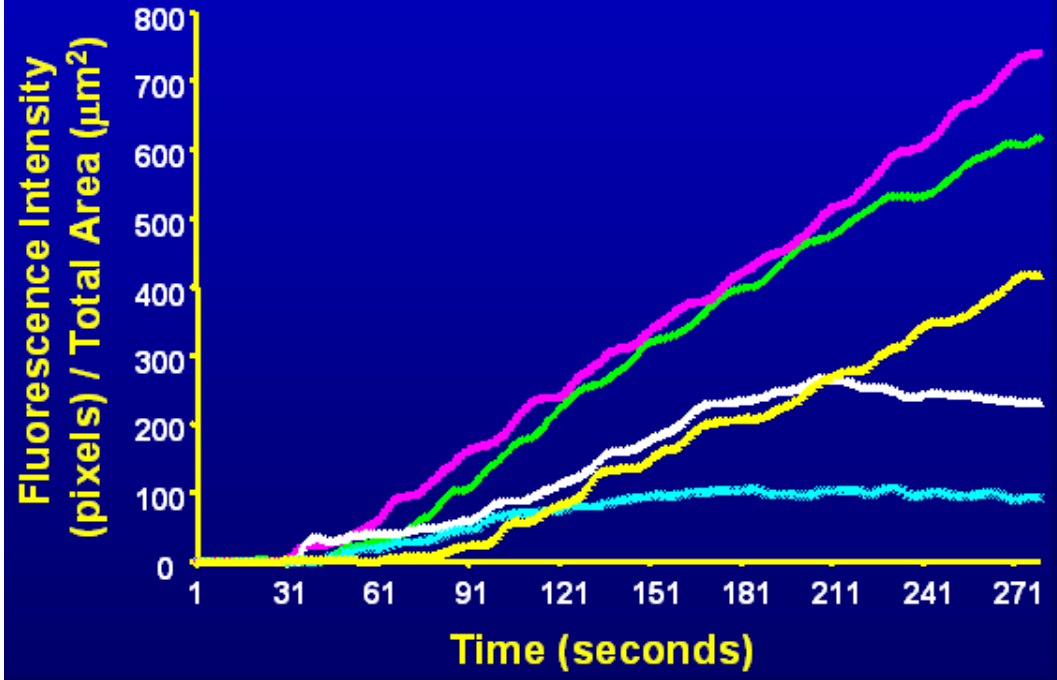


- Real time platelet thrombus formation in collagen coated capillary tube under shear (1600 sec^{-1}) in presence of Xa inhibitor
- Simulates moderate stenosis
- No added agonist
- Platelets labeled with rhodamine 6G
- PRT 128 is a small molecule, non-nucleotide, direct acting, competitive antagonist for $P2Y_{12}$ receptor

Portola Pharmaceuticals Inc.

PRT060128 Effect in Patients with HPR* on Clopidogrel and Aspirin

* ≥ 43% 5 μM ADP-induced Aggregation



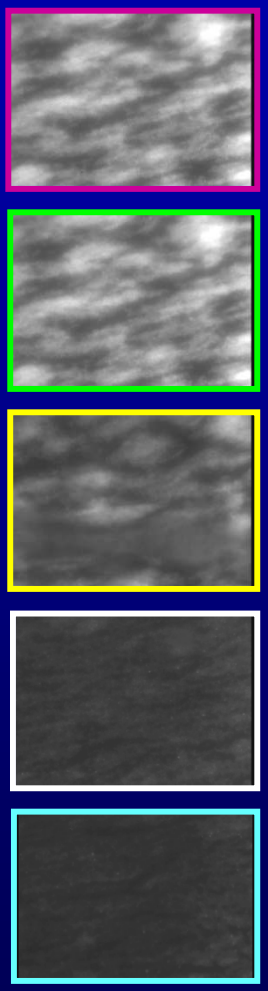
75mg CLP

150mg CLP

24 Hr Post PRT 128

4hr Post PRT 128

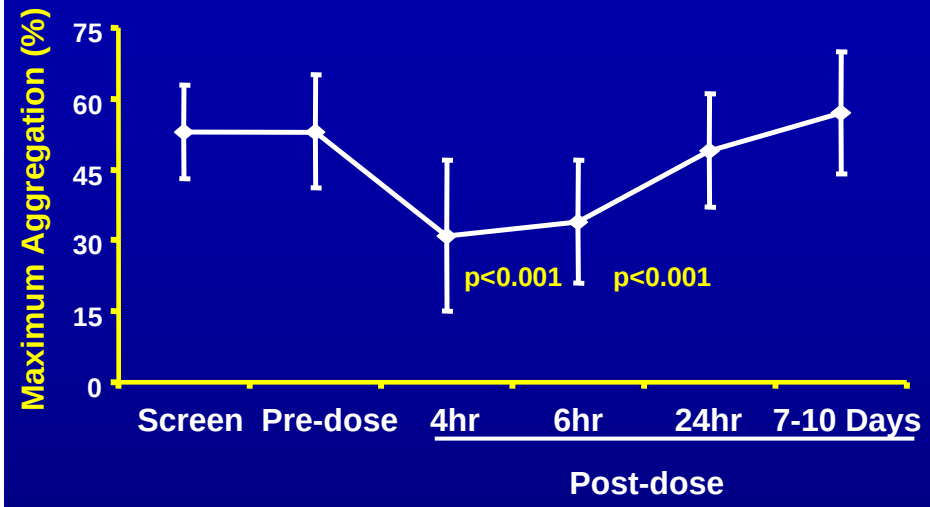
6hr Post PRT 128



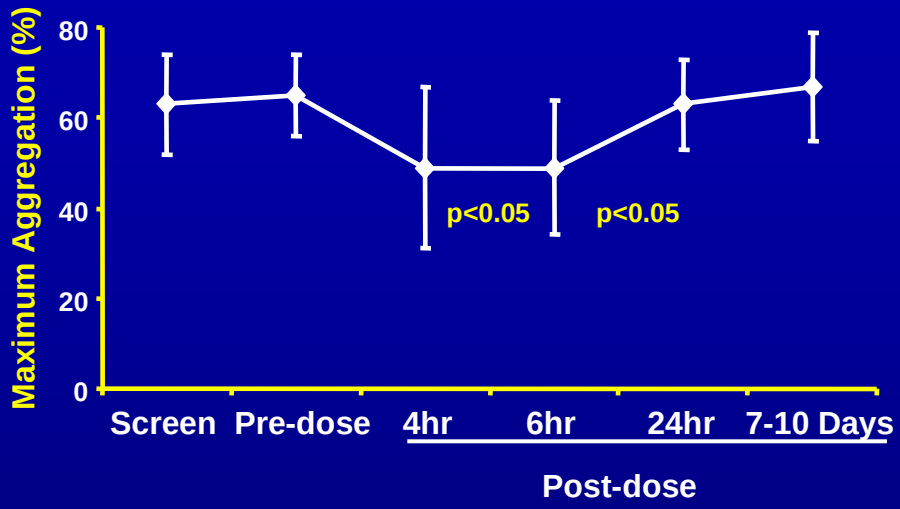
Results

p values vs. baseline

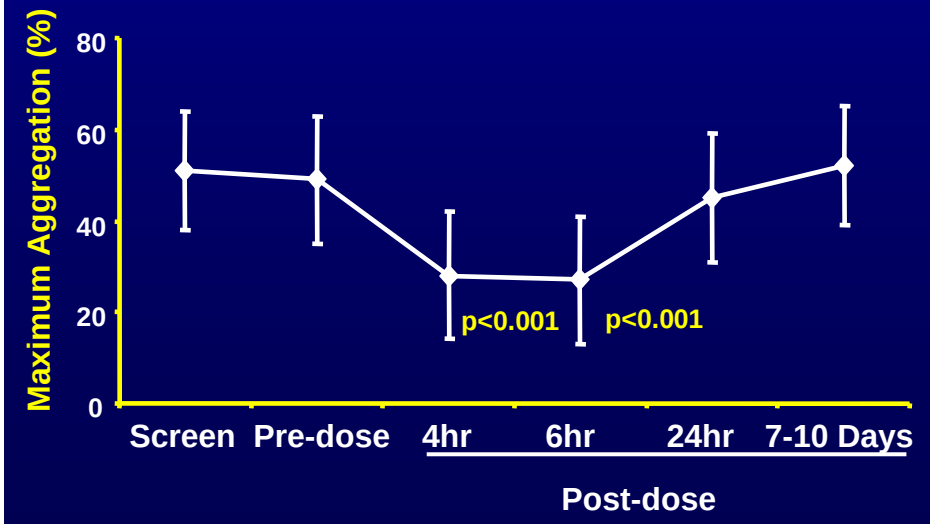
5μM ADP-Induced Aggregation



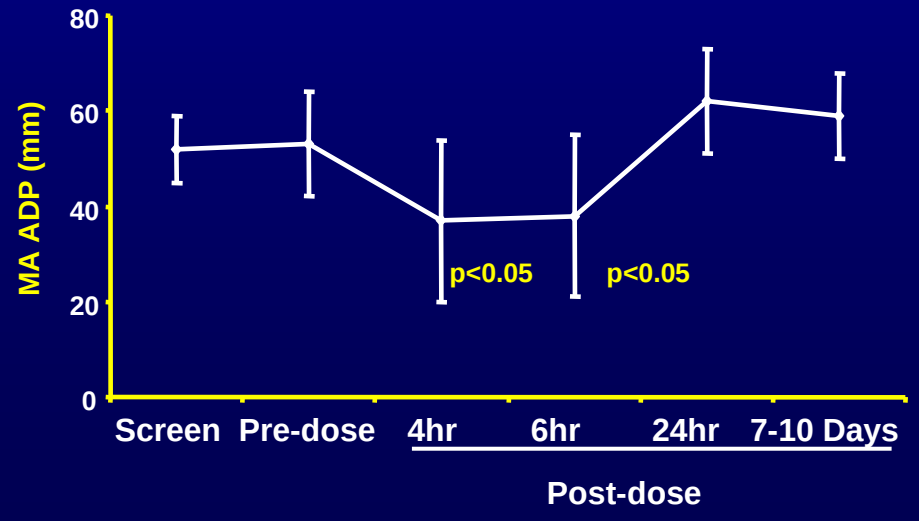
20μM ADP-Induced Aggregation



10μM ADP-Induced Aggregation

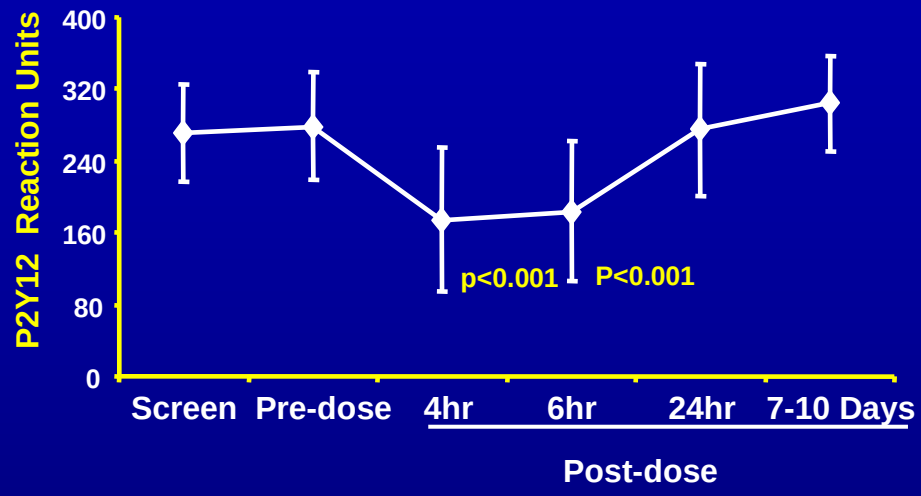


TEG - 2μM ADP-Induced Clot Strength

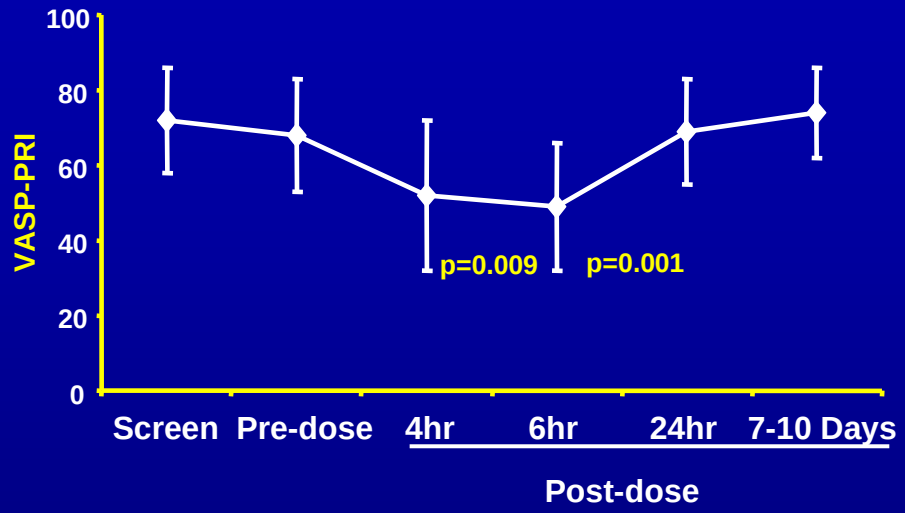


Results

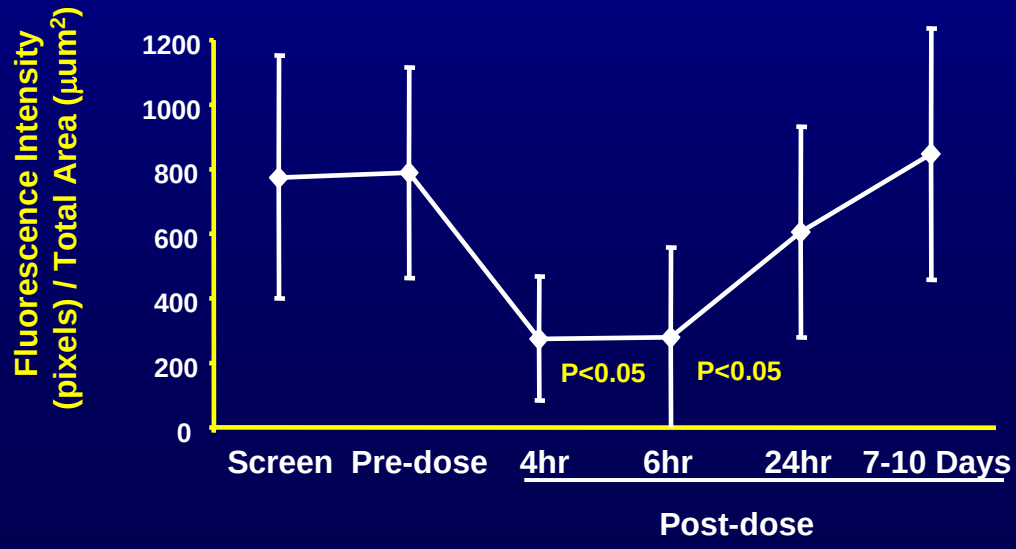
VerifyNow P2Y12 Assay



VASP-Platelet Reactivity Index



Perfusion Chamber Analysis



p values vs. baseline

Conclusions

- First study specifically designed to overcome HPR in patients on standard clopidogrel and aspirin therapy by use of an alternative $P2Y_{12}$ inhibitor.
- HPR accompanying standard maintenance dose clopidogrel therapy is rapidly and reversibly overcome by a single 60 mg oral dose of PRT060128.
- A good correlation was present between peak plasma concentrations of PRT060128 and the observed pharmacodynamic inhibition in all assays.
- Based on these desirable pharmacodynamic properties, PRT060128 has promise as an important future antiplatelet agent.

Sinai Center for Thrombosis Research Team