

On the Metabolism of Prasugrel

Sobre el metabolismo de prasugrel

To the Editor,

We read with interest the editorial by Drs. Freedman and lafrati¹ recently published in *Revista Española de Cardiología*. The editorial mentions that prasugrel is an inhibitor of the P2Y₁₂ receptor, that it is not metabolized in the liver, and that it does not appear to be affected by the variability of isozyme P450. We believe that it might be a good idea here to indicate the pharmacokinetic characteristics of prasugrel.

Prasugrel (CS-747, LY-640315) is a third generation, orally administered thienopyridine that acts as a specific and irreversible antagonist of the 5'-diphosphate (ADP) P2Y₁₂ receptor, and which needs to be metabolized for it to exert its effect.^{2–4} The initial molecule, prasugrel, is rapidly hydrolyzed by intestinal and blood esterases to the metabolite thiolactone (R-95913) (Fig. 1). Thus, prasugrel is not detected in the plasma. Via the action of

cytochrome P450 (CYP), this intermediate metabolite is turned into the active metabolite R-138727, which bonds covalently and irreversibly to receptor P2Y₁₂.^{2,3}

This active metabolite of prasugrel reaches its peak in the plasma after about 30 min and in a manner proportional to the dose given (between 5 mg and 60 mg). When it does not bind to the platelets its half life is about 7 h. It should be remembered that the CYP enzymes involved in the metabolism of clopidogrel and prasugrel are polymorphic, ie, they differ between individuals, which partly accounts for the wide variation seen between patients in their response to clopidogrel.^{3,4}

The metabolism of prasugrel differs from that of clopidogrel in that the metabolism of the latter renders inactive close to 85% of the drug absorbed and two passes through the liver are required (CYP), which influences the variation in individual response.² In contrast, prasugrel is more efficiently converted into its active metabolite via a process of hydrolysis led by carboxyesterases (mainly intestinal), followed by a single pass through the hepatic CYP (3A4, 2B6, 2C9, 2C19) step. This partly explains its greater bioavailability and more efficient antiaggregant effect compared to clopidogrel.⁵

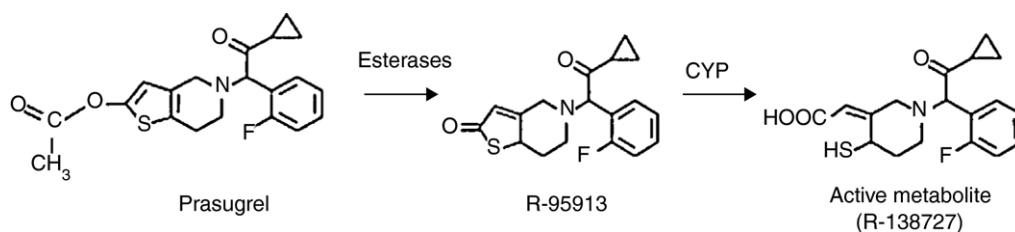


Figure 1. Structural changes required for the activation of prasugrel.

Carlos Felipe Barrera-Ramírez, Luis Ramón Pineda-Pompa, and Carlos E. Guzmán-Rodríguez

División de Cardiología Intervencionista y Hemodinamia, Centro Hospitalario La Concepción, Saltillo, Coahuila, Mexico

* Corresponding author:

E-mail address: carlosfbarrera@yahoo.com (C.F. Barrera-Ramírez).

Available online 16 April 2011

REFERENCES

1. Freedman JE, lafrati HF. Uso de la genética y la transcriptómica en el diagnóstico y tratamiento de la enfermedad coronaria. *Rev Esp Cardiol*. 2010;63:1123–6.

2. Wiviott SD, Antman EM, Braunwald E. Prasugrel Circulation. 2010;122:394–403.

3. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. *Circulation*. 2009;119:2553–60.

4. Mega JL, Wiviott SD, Sabatine MS. Cytochrome P-450 polymorphisms and response to clopidogrel: reply. *N Engl J Med*. 2009;360:2251.

5. Angiolillo DJ, Ferreiro JL. Inhibición del receptor plaquetario P2Y₁₂ de adenosina difosfato plaquetario: efectos beneficiosos y limitaciones de las estrategias terapéuticas actuales y perspectivas futuras. *Rev Esp Cardiol*. 2010;63:60–76.

doi:10.1016/j.rec.2010.11.019

SEE RELATED ARTICLE:

DOI: 10.1016/S1885-5857(10)70225-5

Paravalvular Regurgitations and Percutaneous Prosthetic Aortic Valves

Regurgitaciones paravalvulares y prótesis aórticas percutáneas

To the Editor,

We have read with great interest the study published by León et al.,¹ in which the authors report the reduction in paravalvular regurgitations and in left ventricular hypertrophy, according to echocardiography, one month after percutaneous implantation of

the CoreValve prosthesis in a group of 22 patients. The former effect is attributed to the self-expandability of the prosthesis and the latter to its excellent hemodynamic profile.

We would like to make a few observations on the basis of our own experience. In our center, between April 2008 and December 2010, 144 prostheses were implanted in patients with severe aortic valve disease—mean age, 79.6 ± 6 years; logistic EuroSCORE, 20 ± 14%—who underwent Doppler echocardiography prior to implantation, on the third day and 6 and 12 months postimplantation. After a mean follow-up of 11.6 ± 8 months, we could confirm the excellent hemodynamic profile of the prosthesis, with peak and mean gradients of 15.9 ± 6 mmHg and 8.8 ± 4 mmHg, respectively, as well