

EDITORIAL COMMENT

Coronary Flow Reserve With a Turbo



A Warning for the Use of Adenosine as a Provocative Test in Patients Receiving Ticagrelor?*

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The paper by Bonello et al. (1), published in this issue of the *Journal*, is the first human study investigating the effect of ticagrelor on adenosine plasma concentration in patients with acute coronary syndrome.

Ticagrelor is a new antiplatelet drug directly blocking P2Y₁₂-adenosine diphosphate (ADP) receptors, which show a better clinical profile compared to clopidogrel in patients with acute coronary syndrome (2). As for other popular drugs, a “pleiotropic” non-platelet-directed property has been suggested to explain the favorable clinical results.

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This work was inspired by 2 recently published reports (3,4) supporting the hypothesis of an adenosine-mediated or adenosine-like property of ticagrelor: an animal experiment by van Giezen et al. (3) and a study on healthy volunteers by Wittfeldt et al. (4).

Bonello et al. (1) hypothesize that the pleiotropic effect of ticagrelor may be due to the physiological properties of adenosine. In fact, adenosine increases coronary blood flow by a direct dilation of the microcirculation, which may play a double role in coronary syndromes: 1) in the acute phase, it may have a protective effect on ischemic myocardium (5); and 2) in the long run, it may sustain stent patency.

In the study by Bonello et al. (1), patients receiving ticagrelor had significantly higher adenosine plasma concentration compared to patients receiving clopidogrel. Neither drug had a direct impact on adenosine receptors or on cyclic adenosine monophosphate production, but it was clear that ticagrelor inhibited adenosine reuptake by red blood cells. Higher adenosine plasma concentration may contribute to a better reflow, but also produces side effects

(namely, bradycardia and dyspnea) which, according to the PLATO (Platelet Inhibition and Patient Outcomes) study, are found more frequently with ticagrelor compared to clopidogrel (2).

Therefore, it appears that oral administration of ticagrelor mimics the effect of dipyridamole. Dipyridamole is a first-generation antiplatelet drug that also inhibits re-uptake of adenosine. Adenosine is clinically used for interruption of supraventricular tachycardia (6) and for measurement of coronary artery flow reserve with transthoracic coronary Doppler ultrasound (7). Dipyridamole is also administered during myocardial scintigraphy and stress echocardiography. Dipyridamole is known since 1986 to strongly potentiate the effects of adenosine, including its side effects (8,9). We have confirmed this interaction in our laboratory: in patients pre-treated with very low-dose intravenous dipyridamole (0.14 mg/kg over 1 min), a 4- to 5-fold dose reduction of adenosine is sufficient to elicit maximal coronary vasodilation (unpublished data) (Fig. 1). Interestingly, even oral administration of dipyridamole may potentiate the effect of adenosine (8). In patients receiving dipyridamole, 1.0 ± 0.52 mg adenosine was sufficient to terminate supraventricular tachycardia, whereas 8.8 ± 2.6 mg was needed for patients not receiving dipyridamole (8).

In addition to the important information on the possible pleiotropic effect of ticagrelor related to adenosine concentration, this work may have important implications in our daily clinical practice. It may be hypothesized that patients receiving either ticagrelor or dipyridamole may have

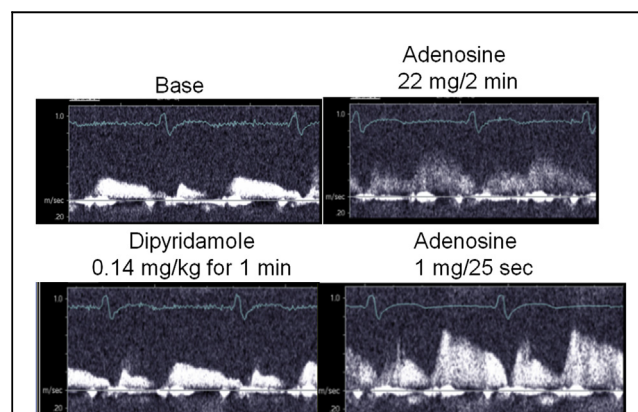


Figure 1 Transthoracic Coronary Doppler Ultrasound in 78-kg Patient With Normal LAD at Coronary Angiography

(Upper panels) Coronary flow reserve of left anterior descending coronary artery (LAD) elicited by standard adenosine dose (140 μ g/kg over 2 min, corresponding to a total dose of 22 mg). (Lower panels) Pre-medication with low-dose dipyridamole (0.14 mg/kg over 1 min) followed by 4-min pause and low-dose adenosine infusion (1 mg over 25 s), which is approximately one-fifth of the standard dose, after correction for the different time of administration (25 s vs. 2 min). At these low doses, neither dipyridamole nor adenosine alone has any biological effect. However, the infusion of low-dose adenosine after dipyridamole produces a similar or even higher coronary hyperemic response compared to standard full-dose adenosine infusion, demonstrating the strong potentiation effect of dipyridamole on adenosine.

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a supernormal response to standard adenosine doses used for both therapeutic and diagnostic applications. For these patients, we may suggest reducing the initial adenosine dose 4-fold to 5-fold, to prevent exaggerated side effects. In light of this new important information, a warning may be suggested regarding the use of adenosine for patients receiving ticagrelor.

A final note: Could the old, cheap, and neglected dipyridamole have the same long-term effect on stent patency as the new and expensive ticagrelor?

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