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Ticagrelor Enhances Adenosine-Induced Coronary Vasodilatory Responses in Humans

Ann Wittfeldt, MD,* Håkan Emanuelsson, MD, PhD,† Gunnar Brandrup-Wognsen, MD, PhD,*† J. J. J. van Giezen, PhD,† Jenny Jonasson, PhD,† Sven Nylander, PhD,† Li-Ming Gan, MD, PhD*†

Göteborg and Mölndal, Sweden

Objectives This study was undertaken to determine if ticagrelor augments adenosine-induced coronary blood flow and the sensation of dyspnea in human subjects.

Background Ticagrelor is a $P2Y_{12}$ receptor antagonist that showed superior clinical benefit versus clopidogrel in a phase III trial (PLATO [Platelet Inhibition and Patient Outcomes]). Ticagrelor has been shown to inhibit cell uptake of adenosine and enhance adenosine-mediated hyperemia responses in a dog model.

Methods In this double-blind, placebo-controlled study, 40 healthy male subjects were randomized to receive a single dose of ticagrelor (180 mg) or placebo in a crossover fashion. Coronary blood flow velocity (CBFV) was measured by using transthoracic Doppler echocardiography at rest after multiple stepwise adenosine infusions given before and after study drug, and again after the infusion of theophylline.

Results Ticagrelor significantly increased the area under the curve of CBFV versus the adenosine dose compared with placebo ($p = 0.008$). There was a significant correlation between ticagrelor plasma concentrations and increases in the area under the curve ($p < 0.001$). In both treatment groups, the adenosine-induced increase in CBFV was significantly attenuated by theophylline, with no significant differences between subjects receiving ticagrelor or placebo ($p = 0.39$). Furthermore, ticagrelor significantly enhanced the sensation of dyspnea during adenosine infusion, and the effects were diminished by theophylline.

Conclusions Ticagrelor enhanced adenosine-induced CBFV and the sensation of dyspnea in these healthy male subjects via an adenosine-mediated mechanism. (Study to Assess the Effect of Ticagrelor on Coronary Blood Flow in Healthy Male Subjects; NCT01226602) (J Am Coll Cardiol 2013;61:723–7) © 2013 by the American College of Cardiology Foundation

Ticagrelor, a novel, oral, direct-acting, reversibly binding $P2Y_{12}$ receptor antagonist, is approved for the treatment of patients with acute coronary syndrome (1). In the PLATO (Platelet Inhibition and Patient Outcomes) trial, ticagrelor significantly reduced the incidence of myocardial infarction, stroke, or death from vascular causes, compared with standard treatment with clopidogrel (2). In the same study, dyspnea and asymptomatic ventricular pauses were more common in patients receiving ticagrelor than in those receiving clopidogrel.

It has been shown that ticagrelor can inhibit adenosine cell uptake, likely through inhibition of the equilibrative nucleoside transporter 1 (3). Ticagrelor also significantly and dose dependently augmented adenosine-mediated coronary blood flow increases in a dog model (3). These findings could suggest increased local adenosine levels in patients treated with ticagrelor because both dyspnea and ventricular pauses are known effects of adenosine (4,5).

The goal of the current study was to determine if ticagrelor, at a clinically relevant dose, can augment adenosine-induced physiological responses, coronary blood flow velocity (CBFV), and dyspnea in healthy human subjects.

Methods

The study was approved by the Regional Ethical Review Board in Gothenburg, Sweden, and was conducted in accordance with the Declaration of Helsinki. Data management and monitoring were performed by Quintiles AB, Uppsala, Sweden.

Study population. Forty healthy male subjects age 18 to 40 years with a body mass index of 18 to 30 kg/m^2 and weighing 50 to 100 kg provided written informed consent before participating in the study.

From the *Department of Clinical and Molecular Medicine, Institution of Medicine, Sahlgrenska Academy, Göteborg University, Göteborg, Sweden; and †AstraZeneca R&D, Mölndal, Sweden. This study was supported by AstraZeneca. All authors except Dr. Wittfeldt are employees of AstraZeneca. Dr. Emanuelsson is owner of shares in AstraZeneca. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Abbreviations and Acronyms

AUC = area under the curve
CBFV = coronary blood flow velocity
CI = confidence interval
CV% = coefficient of variation
LAD = left anterior descending coronary artery

Study design. This was a double-blind, placebo-controlled, crossover study. After screening, subjects were randomized to receive ticagrelor (180 mg) or placebo. After a washout period of 6 to 21 days, subjects received the alternative regimen (Fig. 1A). They underwent an overnight fast and were required to abstain from caffeine for 24 h before study drug administration.

Subjects received multiple intravenous adenosine infusions with the use of a stepwise dosing protocol: 0, 50, 80, 110, and 140 μg/kg/min (Fig. 1B). Adenosine infusions were given predose, repeated 2 h postdose, and again 10 min after a 20-min intravenous infusion of theophylline (5 mg/kg).

Assessments. CBFV. CBFV was measured in the left anterior descending coronary artery (LAD) before and during the different adenosine infusions (ITEM Development AB, Stocksund, Sweden) by using a Siemens Acuson platform equipped with a 4V1C transducer with 3.5 MHz color and 1.75 MHz spectral Doppler frequency (Acuson Sequoia 512, Siemens, Mountain View, California) (6). To ensure CBFV was measured in the same LAD segment, trough repeated measurements, the surface anatomic position, degree of rotation of the transducer, and the LAD position relative to the left ventricle were carefully documented at the first visit. Cine loops and Doppler images were stored for offline measurements by using Image Arena 2.9.1 (TomTec Imaging Systems GmbH, Unterschleissheim, Germany). Mean diastolic flow velocity was calculated by manually tracing the diastolic flow velocity signal. Baseline CBFV values were calculated by using the mean value of 3 representative heart beats. The mean hyperemic CBFV for each adenosine dose was calculated as the mean of the 3 highest CBFV values.

TICAGRELOR EXPOSURE. Plasma concentrations of ticagrelor and its main circulating metabolite, AR-C124910XX, were measured in venous blood collected 2 h postdose. After protein precipitation, plasma concentrations of ticagrelor and AR-C124910XX were analyzed by using liquid chromatography mass spectrometry. The lower limits of quantification for ticagrelor and AR-C124910XX were 5 and 2.5 ng/ml, respectively (7).

DYSPNEA. Subjects were trained to self-report the sensation of dyspnea after each adenosine dose by using the Borg scale; the scale is scored from 1 (no sensation of dyspnea) to 10 (maximum sensation of dyspnea).

Statistical analysis. All data were summarized by using SAS version 8.02 and R version 2.13.0. The effect of ticagrelor compared with placebo on the area under the curve (AUC) of CBFV versus the adenosine dose (primary endpoint) was estimated by using a mixed-model analysis of variance. The model included the log AUC change with ticagrelor and placebo as the response variable; the log pre-dose

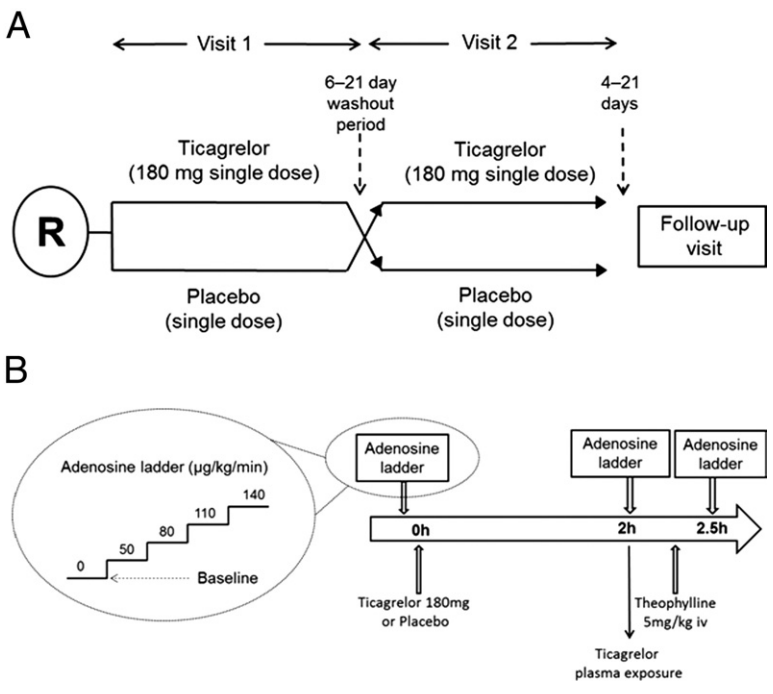

Figure 1 Study Design and Procedure

(A) Study design and **(B)** the procedures performed at visits 1 and 2. IV = intravenous; R = randomization.