Serum uric acid levels during dual antiplatelet therapy with ticagrelor or clopidogrel: Results from a single-centre study

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Abstract *Background and aims:* New antithrombotic therapies have significantly improved the outcomes of patients with acute coronary syndrome (ACS), where the introduction of ticagrelor has provided the greatest mortality benefits. However, ticagrelor treatment has been associated with a potential increase in the serum uric acid (SUA) levels, which may influence endothelial dysfunction and prothrombotic status, thereby affecting the risk of acute cardiovascular events in patients requiring dual antiplatelet therapy (DAPT). The present study aimed to compare the impact of antiplatelet agents such as ticagrelor or clopidogrel on SUA levels and their effect on platelet reactivity.
Methods and results: We included patients admitted for ACS or elective percutaneous coronary intervention (PCI) and discharged with ASA (acetylsalicylic acid; 100–160 mg) and clopidogrel (75 mg) or ticagrelor (90 mg twice a day). Chemistry was assessed at admission (baseline) and after a 30–90-day period of DAPT (together with platelet reactivity). The absolute and percentage variations of SUA after DAPT introduction were considered. Multiple-electrode aggregometry was used to assess platelet function.

A total of 378 patients were enrolled, with 145 treated with aspirin and clopidogrel (AC) and 233 with aspirin and ticagrelor (AT). The AC patients were older ($p = 0.003$) and more often showed elective PCI as an indication to DAPT (<0.001); they received chronic therapy with ARB (angiotensin II receptor blocker; $p = 0.001$), nitrates ($p = 0.044$), CCB (calcium channel blocker; $p = 0.005$) and diuretics ($p = 0.044$). The AT patients displayed a higher percentage of ACS diagnosis ($p < 0.001$) and received chronic therapy with ACE (angiotensin-converting enzyme) inhibitors ($p = 0.001$), beta blockers ($p = 0.001$) and statins ($p = 0.013$).

The AC patients displayed higher platelet reactivity at COL (collagen) test, ASPI test and ADP (adenosine diphosphate) test ($p = 0.03$, 0.001 and <0.001, respectively) and a higher percentage of HRPR (high residual platelet reactivity) in the ADP test ($p = 0.001$).

No difference was found in the baseline uric acid and creatinine levels between AC and AT patients. At 30–90 days, a significant absolute and percentage increase in the SUA levels was found in AT as compared to AC patients (0.204 mg/dl vs. −0.165 mg/dl, $p = 0.034$; 6.26% vs. −0.005%, $p = 0.018$, respectively). Results were not influenced by variations in renal function. At multivariate analysis, in fact, ticagrelor therapy emerged as an independent predictor of increase in the uric acid levels (odds ratio (OR; 95% confidence interval (CI)) = 2.79 (1.66–4.67), $p < 0.001$). However, the variation in the SUA levels did not affect platelet reactivity or HRPR in both AC and AT patients.

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Conclusion: An increase in the SUA levels at 30−90 days was observed in patients receiving chronic DAPT with ticagrelor, but not clopidogrel treatment. However, the changes in the SUA levels do not influence platelet aggregation.

Introduction

The significant innovations achieved in interventional cardiology and medical therapy have not decreased the burden of coronary artery disease (CAD), which still represents a leading cause of mortality [1]. Nevertheless, the introduction of more potent antithrombotic treatments and early reperfusion strategies have dramatically improved the prognosis of patients after an acute coronary event [2−4].

In particular, ticagrelor, a direct inhibitor of platelet P2Y12 receptor, caused a significant reduction in mortality and ischaemic events as compared to clopidogrel, in patients experiencing acute cardiovascular events, due to its more potent and predictable antiplatelet effect, whose benefits have been suggested to increase over time [5,6].

However, a potential warning has been raised since the first clinical studies with ticagrelor, which was associated with an increase in serum uric acid (SUA) levels, not observed in clopidogrel-treated patients [7]. In fact, elevated SUA levels have been associated with the development and progression of CAD [1], by modulating endothelial dysfunction, oxidative stress and inflammation [8−10]. Although the independent role of SUA levels in the pathogenesis of CAD remains debatable [11]; their potential impact on thrombosis, platelet hyperreactivity and plaque instability could cause more harmful effects among high-risk patients requiring dual antiplatelet therapy (DAPT) for an acute coronary event.

However, no study, with the exception of PLATO trial, has to date investigated the dynamic changes of SUA levels during DAPT administration and their impact on platelet reactivity among patients with CAD; therefore, the present study focuses on this topic.

Methods

We included patients admitted to the Division of Cardiology, "Maggiore della Carità" Hospital, Eastern Piedmont University in Novara, Italy, from September 2011 to April 2015 requiring DAPT for acute coronary syndrome (ACS) or undergoing elective percutaneous coronary intervention (PCI). An invasive treatment with coronary angiography and eventual coronary stenting was not a required inclusion criterion. All patients receiving at discharge DAPT with ASA (acetylsalicylic acid; 100−160 mg daily) and an ADP (adenosine diphosphate) antagonist (clopidogrel 75 mg daily or ticagrelor 90 mg b.i.d) were scheduled for chemistry and platelet function test evaluation within a period ranging from 30 to 90 days from hospital discharge.

The study was approved by our local ethical committee and informed consent was obtained from all patients. The main demographic, clinical and angiographic data along with the indication for DAPT were recorded at discharge and included in a dedicated database, protected by password. As previously described [12], hypertension was defined as systolic pressure >140 mm Hg and/or diastolic pressure >90 mm Hg or if the individual was taking antihypertensive medications. Diabetes mellitus was defined as previous diagnosis, specific treatment administration (oral drug or insulin) and fasting glycaemia levels >126 mg/dL or HbA1c >6.5% [13]. Chronic renal failure was considered for history of renal failure or an admission glomerular filtration rate (GFR) <60 mol/min/1.73 m^2 by the MDRD (Modification of Diet in renal Disease) formula. The exclusion criteria were patients' refusal or if the patient had given up DAPT.

Biochemical measurements

Blood samples were drawn in the early morning, following a fasting period of 12 h. Glucose, creatinine, glycosylated haemoglobin and lipid profile were determined as previously described [12]. Blood cell count was performed in a blood sample collected in tripotassium EDTA (ethylenediaminetetraacetic acid; 7.2 mg) tubes. These blood samples were analysed within 2 h of venipuncture using an automatic blood cell counter (A Sysmex XE-2100).

Platelet aggregation

Platelet aggregation was determined by Multiplate electrical impedance aggregometry (MEA). The aggregation tests were performed at >30 min and within 2 h from blood collection, as suggested by the manufacturers [14]. Platelet aggregation was assessed in a multichannel system; platelets in separate cuvettes could be stimulated either with ADP (6.4 μM + 20 μl prostaglandin E1), collagen (3.2 μg/ml; COL test), arachidonic acid (AA; 0.5 mM) or thrombin receptor-activating peptide (TRAP-6; 30 μM). Results were expressed as arbitrary aggregation units (AU) and plotted against time and platelet function was defined as the area under curve (AUC or AU*min). High residual platelet reactivity (HRPR) for clopidogrel/ticagrelor was defined for ADP test above 417 AU*min,