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Impact of ticagrelor administration strategy on its pharmacokinetics and pharmacodynamics in patients with unstable angina pectoris: a protocol of a randomized study

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ABSTRACT

Introduction. Dual antiplatelet therapy with aspirin and a P2Y12 receptor inhibitor constitutes an essential part of the management of patients with acute coronary syndromes (ACS). Based on the favorable results of the PLATO trial, ticagrelor is currently recommended as the first line P2Y12 receptor inhibitor in a broad spectrum of ACS patients. According to the recently published data, several conditions, including concurrent analgesia with morphine and clinical presentation as an ACS, may alter ticagrelor absorption and its antiplatelet effect. Therefore, the goal of the present study was to investigate pharmacokinetics and pharmacodynamics of new ticagrelor administration strategies aimed to overcome limitations of the standard ticagrelor loading regimen.

Methods/design. The study is designed as a phase IV, single center, randomized, investigator-initiated, parallel-group, open-label, interventional study comparing the influence of various ticagrelor administration strategies on its pharmacokinetics and pharmacodynamics. Patients with unstable angina pectoris will be randomized in a 1:1:1 ratio into one of three arms, each receiving a 180 mg ticagrelor loading dose (LD). Ticagrelor administration strategies comprise: 1) pulverized ticagrelor administered sublingually, 2) pulverized ticagrelor in 10 mL suspension in tap water administered orally and 3) integral ticagrelor tablets administered orally. An internal pilot study including 30 (10 in each of the arms) is planned in order to determine the final sample size. The primary endpoint of the trial is time (t_{max}) required for ticagrelor and its active metabolite AR-C124900XX to reach maximum plasma concentration within time frame of six hours after administration of ticagrelor LD. The secondary endpoints include ticagrelor and AR-C124900XX maximum plasma concentration, area under the plasma concentration-time curve for ticagrelor and AR-C124900XX (AUC 0–6h) and platelet reactivity assessed with Multiple Electrode Aggregometry using the Multiplate™ Analyzer prior to and within time frame of six hours following ticagrelor LD.

Discussion. This study is expected to provide essential evidence-based data on the impact of ticagrelor administration strategy on its pharmacokinetics and pharmacodynamics in patients with unstable angina pectoris. Hopefully, based on its results, further clinical outcome-powered trials on new ticagrelor administration strategies will be designed and conducted.

Key words: ticagrelor administration, ACS, pharmacokinetics, pharmacodynamics, angina

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Introduction

Based on the guidelines of the European Society of Cardiology (ESC), antiplatelet therapy comprising aspirin and a P2Y12 receptor inhibitor is a recommended regimen for patients with acute coronary syndromes (ACS) [1, 2]. Clinical advantages of either ticagrelor or prasugrel over clopidogrel have been proven in large clinical trials, such as the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibitioN with prasugrel-Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) or PLATelet inhibition and patient Outcomes (PLATO) studies, thus making these agents preferable P2Y12 receptor inhibitors in ACS patients [3–9]. Importantly, ticagrelor is currently recommended as the first line P2Y12 receptor inhibitor in a broad spectrum of ACS patients, also in subjects managed conservatively and in patients who are likely to undergo coronary artery bypass surgery, in the subsets where prasugrel should be avoided [1].

It is believed that adequate platelet inhibition is crucial during percutaneous coronary intervention (PCI) and in the periprocedural period, particularly in patients undergoing coronary stenting, because implantation of thrombogenic stent into the thrombotic lesion exposes patients to the risk of stent thrombosis, a potentially fatal complication. Therefore, routine immediate administration of antiplatelet agents, just after making the initial diagnosis, is recommended in all ACS patients with the exception of prasugrel, which should not be given in subjects with non-ST elevation ACS until coronary angiography is completed [1].

Notably, morphine is considered a drug of choice for chest pain alleviation in patients presenting with acute myocardial infarction [2]. Nevertheless, based on the available data, morphine, an opioid analgesic, may lead to decreased clopidogrel plasma concentration and its attenuated antiplatelet action if both drugs are administered simultaneously [10]. Additionally, our recent randomized study indicated that morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction [11–13]. Similarly, morphine was also demonstrated to decrease ticagrelor concentrations, but not its antiplatelet effects, in healthy volunteers [14]. Besides morphine co-administration, other clinical conditions (e.g. clinical presentation with an ACS, particularly ST-segment elevation myocardial infarction (STEMI), concomitant cardiogenic shock, unconsciousness, incapability to swallow, malabsorption, therapeutic hypothermia) may reduce absorption of P2Y12 receptor inhibitors and/or their antiplatelet action [15–18].

Interestingly, Zafar et al. demonstrated higher bioavailability of crushed vs. integral clopidogrel tablets in healthy volunteers [19]. Similarly, administration of pulverized vs. integral ticagrelor tablets was associated with increased antiplatelet effect in STEMI patients in the Mashed Or Just Integral pill of TicagrelOr (MOJITO) study [20].

These reports provide a solid rationale for new ticagrelor administration strategies, which may overcome limitations of the standard ticagrelor loading regimen. Thus, we designed a study evaluating differences in ticagrelor pharmacokinetics and pharmacodynamics in patients who received pulverized tablets either orally or sublingually in comparison with conventional oral administration of integral tablets.

Methods

The trial is designed as a phase IV, single center, randomized, investigator-initiated, parallel-group, open-label, interventional study aimed to evaluate the influence of ticagrelor administration strategies on its pharmacokinetics and pharmacodynamics in patients hospitalized for unstable angina pectoris. The protocol of the study was approved by The Ethics Committee of Nicolaus Copernicus University in Toruń, Ludwik Rydygier Collegium Medicum in Bydgoszcz (approval number KB 540/2015). The study is conducted in compliance with the regulations established in the Declaration of Helsinki. Each participant needs to sign a written informed consent before enrollment into the trial. The eligibility criteria for enrollment into the study include male and non-pregnant female patients in the age range of 18–80 years, diagnosed with unstable angina pectoris whose mortality risk score was assessed < 140 points according to GRACE Score, who signed a written consent for coronary angiography PCI, if needed. Key exclusion criteria include ongoing (or terminated within 14 preceding days) treatment with any P2Y12 receptor inhibitor, treatment with oral or parenteral anticoagulants, history of intracranial hemorrhage or recent (defined as last 30 days) gastrointestinal hemorrhage, coagulation disorders, severe chronic pulmonary disorders, second or third degree atrioventricular block, Killip class III or IV on the point of screening. The full list of inclusion and exclusion criteria is presented in Table 1.

The study site is The Department of Cardiology, Antoni Jurasz University Hospital in Bydgoszcz, Poland. Patients diagnosed with unstable angina pectoris who signed the informed consent, are subsequently randomized in a 1:1:1 manner into one of three arms each receiving a 180 mg ticagrelor loading dose (LD). Ticagrelor administration strategies comprise: 1) pulverized ticagrelor administered sublingually, 2) pulverized

Table 1. The complete list of inclusion and exclusion criteria used in the study

Inclusion criteria	Exclusion criteria
Provision of informed consent prior to any study specific procedures	Treatment with ticlopidine, clopidogrel, prasugrel or ticagrelor within 14 days before the study enrollment
Clinical diagnosis of unstable angina	Hypersensitivity to ticagrelor
Male or non-pregnant female, aged 18–80	Current treatment with oral anticoagulant or chronic therapy with low--molecular-weight heparin
Provision of informed consent for angiography and percutaneous coronary intervention (PCI)	Active bleeding
GRACE score < 140 pts	History of intracranial hemorrhage
	Recent gastrointestinal bleeding (within 30 days)
	History of coagulation disorders
	Platelet count less than <100 × 10^3/mcL
	Hemoglobin concentration less than 10.0 g/dL
	History of moderate or severe hepatic impairment
	History of major surgery or severe trauma (within 3 months)
	Patients considered by the investigator to be at risk of bradycardic events
	Second or third degree atrioventricular block during screening for eligibility
	History of asthma or severe chronic obstructive pulmonary disease
	Patient requiring dialysis
	Manifest infection or inflammatory state
	Killip class III or IV during screening for eligibility
	Respiratory failure
	History of severe chronic heart failure (NYHA class III or IV)
	Concomitant therapy with strong CYP3A inhibitors (ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin, nefazadone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir) or strong CYP3A inducers (rifampicin, phenytoin, carbamazepine, dexamethasone, phenobarbital) within 14 days and during study treatment
	Body weight below 50 kg

ticagrelor in 10 mL suspension in tap water administered orally and 3) integral ticagrelor tablets administered orally. Randomization is conducted using Random Allocation Software version 1.0. Coronary angiography is performed at least six hours after the enrollment into the trial, after completing the blood sample collecting schedule. The study results will be reported in line with the CONSORT statement [21, 22]. The scheme of the study is presented in Figure 1.

Endpoints

The primary endpoint of the trial is time (t_{max}) required for ticagrelor and its active metabolite AR-C124900XX to reach maximum plasma concentration within time frame of six hours after administration of ticagrelor LD. The secondary endpoints include ticagrelor and AR-C124900XX maximum plasma concentration, area under the plasma concentration-time curve for ticagrelor and AR-C124900XX (AUC 0–6h) and platelet reactivity assessed with Multiple Electrode Aggregometry (MEA) using the Multiplate™ Analyzer prior to and within time frame of six hours following ticagrelor LD. All the study endpoints together with details regarding sampling are listed in Table 2.

Blood sample collection

Blood collection using an intravenous catheter is scheduled directly prior to ticagrelor LD and 15, 30, 45, 60, 120, 180, 240, 360 minutes following LD. Blood collection is performed by cardiology intensive care nurses and is supervised by the physician responsible for previous eligibility screening for each patient.

Pharmacokinetics and pharmacodynamics

Pharmacokinetic assessments of all blood samples obtained according to the schedule are performed in The Department of Medicinal Chemistry, Nicolaus Copernicus University, Ludwik Rydygier Collegium Medicum in Bydgoszcz. Concentration of ticagrelor and its active metabolite (AR-C124910XX) are determined with liquid chromatography tandem mass spectrometry. Pharmacodynamic measure-

ments for the sake of the trial are performed using Multiple Electrode Aggregometry (MEA; the Multiplate™ Analyzer, Roche Diagnostics International Ltd, Rotkreuz, Switzerland). MEA will be used in all enrolled participants. Pharmacokinetic and pharmacodynamic analyzes are performed by blinded skilled investigators. Both methods have been described in details previously [11, 12, 23–25].

Pilot study

We plan to perform an internal pilot study including 30 (10 in each of the arms) in order to determine the final sample size.

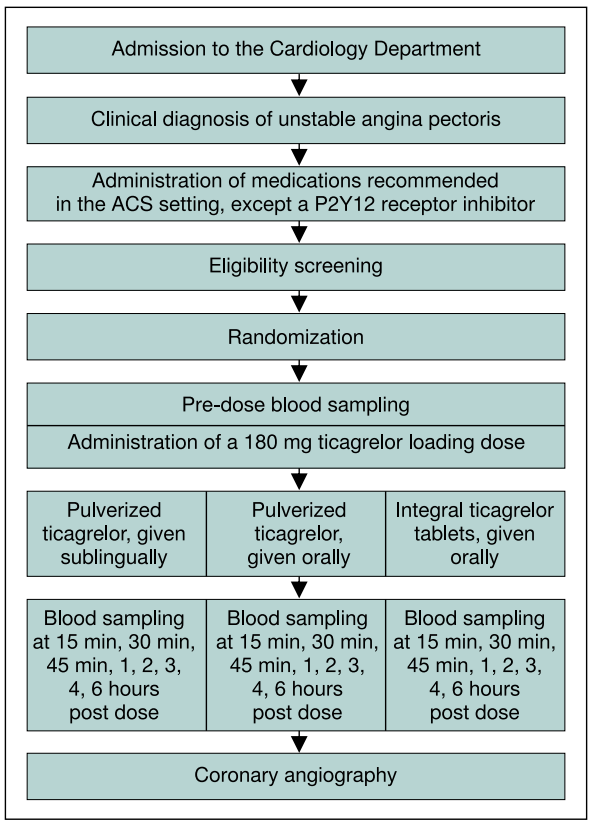

Figure 1. The schematic protocol of the study

Safety of the trial

The study population is limited only to patients diagnosed with unstable angina pectoris, whose mortality risk is low or intermediate, as estimated by the GRACE score (< 140 points). Moreover, all participants receive medications of all other groups recommended by the ESC guidelines for the ACS management, e.g. aspirin, statins, beta-blockers, angiotensin converting enzyme inhibitors or angiotensin II receptor inhibitors. Every case of patient's condition deterioration leading to the necessity of immediate coronary angiography will result in the discontinuation of that patient's participation in the trial so as to ensure appropriate therapy. For the entire hospitalization period, the study participants will receive ticagrelor maintenance dose of 90 mg twice daily with the strong recommendation to continue therapy with ticagrelor after discharge. Ticagrelor may be replaced with clopidogrel (a 600 mg clopidogrel loading dose will be administered) in patients unable to continue such treatment, mainly due to financial reasons, on the day of discharge from The Department of Cardiology.

Discussion

This study is expected to provide essential evidence-based data on the impact of ticagrelor administration strategies on its pharmacokinetics and pharmacodynamics in patients with unstable angina pectoris. Hopefully, based on its results, further clinical outcome-powered trials on new ticagrelor administration strategies will be designed and conducted.

The study status

The study is currently recruiting participants. It was registered in the ClinicalTrials.gov database and received identifier NCT02612116.

Table 2. The list of study endpoints

Primary endpoint of the study	Secondary endpoints of the study
Time to maximum concentration (t_{max}) for ticagrelor and AR-C124900XX [Time frame: 6 hours]	Maximum ticagrelor and AR-C124900XX concentration [Time frame: 6 hours] Area under the plasma concentration-time curve for ticagrelor (AUC 0–6 h) [Time frame: pre-dose and 15 min, 30 min, 45 min, 1, 2, 3, 4, 6 hours post dose] Area under the plasma concentration-time curve for AR-C124900XX (AUC 0–6h) [Time frame: pre-dose and 15 min, 30 min, 45 min, 1, 2, 3, 4, 6 hours post dose] Platelet reactivity assessed by Multiple Electrode Aggregometry [Time frame: pre-dose and 30 min, 1, 2, 3, 4, 6 hours post dose]

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