VIA MEDICA

ORIGINAL ARTICLE

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The influence of metoclopramide on pharmacokinetics and pharmacodynamics of ticagrelor in patients with unstable angina pectoris receiving concomitant treatment with morphine — a protocol of a randomized trial

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ABSTRACT

Introduction. Nowadays, due to the "morphine effect", the screening of methods that provide quick and effective platelet inhibition with oral P2Y12 inhibitors administrated simultaneously with morphine in patients with acute coronary syndromes are extensively investigated by numerous scientists. Metoclopramide, which stimulates the motility of gastrointestinal tract, may become a potential method of overcoming the negative morphine effect. The present study was designed to demonstrate the influence of metoclopramide administration on the pharmacokinetic and pharmacodynamic profile of ticagrelor between patients with unstable angina pectoris treated with morphine and crushed ticagrelor.

Methods/design. A study was designed as a phase IV, single-centre, randomized, investigator-initiated, parallel-group, open-label, interventional trial. Patients will be randomized in a 1:1 manner into two arms: 1) patients treated with a combination of crushed ticagrelor and morphine and 2) patients treated with a combination of crushed ticagrelor followed by morphine and metoclopramide. Blood sample collection will be scheduled directly before the administration of ticagrelor loading dose and 15, 30, 45, 60, 120, 180, 240, and 360 minutes after the loading dose. Pharmacokinetic and pharmacodynamic assessment of ticagrelor and its active metabolite will be evaluated in all pre-defined time points.

Discussion. The current study is, to our knowledge, the first one to provide data on the influence of metoclopramide in patients with acute coronary syndromes, who received intravenous opioid analgesia. It is expected to contribute to the development of contemporary knowledge on the treatment of patients presenting with acute coronary syndromes, and should enable clinicians to implement strategies of quick platelet inhibition.

Key words: crushed ticagrelor, morphine, metoclopramide, pharmacokinetic, pharmacodynamics

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Introduction

Platelets play a key role in acute coronary syndromes (ACS). After atherosclerotic plaque rupture, platelets could form pathogenic, occlusive thrombi, which leads to acute ischaemic events [1]. Current antiplatelet pharmacological therapy relies on administration of aspirin to patients, as well as oral P2Y12 inhibitors. However, according to numerous clinical trials in patients with ACS, the administration of prasugrel or ticagrelor is preferred, compared to clopidogrel [2–5].

In order to relieve pain and anxiety, morphine is a commonly used drug in the acute phase of ACS [6, 7]. Nevertheless, in patients with ST segment elevation

myocardial infarction (STEMI), in which the effective platelet inhibition is required, the delayed onset of platelet inhibition was demonstrated, especially in patients treated with morphine [8–10].

Nowadays, due to the "morphine effect", the screening of methods that provide quick and effective platelet inhibition with oral P2Y12 inhibitors administrated simultaneously with morphine in ACS patients are extensively investigated by numerous scientists. Previously reported studies showed that the administration of crushed ticagrelor increased both ticagrelor and its active metabolite concentration in human plasma [11, 12]. Additionally, in patients treated with crushed ticagrelor, earlier inhibition of platelet aggregation was observed, compared to the reports in which the integral tablets were given [13, 14]. Venetsanos et al. also confirmed that the administration of chewed tablets is feasible and provides faster inhibition than the administration of either crushed or integral tablets [15].

Metoclopramide, as a well-known and commonly used prokinetic drug which stimulates the motility of gastrointestinal tract, may become a potential method of overcoming the negative morphine effect. The present study was designed to demonstrate the influence of metoclopramide administration on the pharmacokinetic and pharmacodynamic profile of ticagrelor between patients with unstable angina pectoris treated with morphine and crushed ticagrelor.

Methods

The study was designed as a phase IV, single-centre, randomized, investigator-initiated, parallel-group, open-label, interventional trial. We plan to evaluate differences in the pharmacokinetic and pharmacodynamic profile of ticagrelor and it active metabolite AR-C1249XX between patients hospitalised for unstable angina pectoris, who received either a combination of crushed ticagrelor and morphine or crushed ticagrelor, morphine, and metoclopramide. The study protocol was approved by the Ethics Committee of Nicolaus Copernicus University in Toruń, Ludwik Rydygier Collegium Medicum in Bydgoszcz and received approval number KB 339/2016. Provision of informed consent will be needed for each patient to enrol in the study.

Eligibility screening will be based on inclusion criteria including, clinical diagnosis of unstable angina pectoris, low-intermediate mortality risk (< 140 pts) assessed with GRACE score, males and non-pregnant females 18–80 years old, informed consent for coronary angiography, and percutaneous coronary intervention if required. Major exclusion criteria comprise concomitant treatment with any P2Y12 receptor inhibitor (or treatment terminated within 14 days preceding the screening), treatment with any opioid "mi" receptor agonist, current use of oral anticoagulants or chronic therapy with low-molecular-weight heparin, active bleeding, history of intracranial haemorrhage, bradycardia, and second- or third-degree atrioventricular block during screening for eligibility. The complete list of inclusion and exclusion criteria used in the study is presented in Table 1.

The study will be performed in the Department of Cardiology, Antoni Jurasz University Hospital No. 1 in Bydgoszcz, Poland. All participants, after providing informed consent, will be randomized in a 1:1 manner into two arms:

Table 1. Complete list of inclusion/exclusion criteria in the study

Inclusion criteria
Provision of informed consent prior to any study-specific procedures
Diagnosis of unstable angina
Male or non-pregnant female, aged 18–80 years
Provision of informed consent for angiography and PCI
GRACE score < 140 pts
Exclusion criteria
Treatment with ticlopidine, clopidogrel, prasugrel, or ticagrelor within 14 days before the study enrolment
Current treatment with morphine or any opioid "mi" receptor agonist
Hypersensitivity to ticagrelor
Current treatment with oral anticoagulant or chronic therapy with low-molecular-weight heparin
Active bleeding
History of intracranial haemorrhage
Recent gastrointestinal bleeding (within 30 days)
History of coagulation disorders
Platelet count less than $< 100 \times 10^3/\mu L$
Haemoglobin concentration less than 10.0 g/dL
History of moderate or severe hepatic impairment
History of major surgery or severe trauma (within 3 months)
Risk of bradycardic events as judged by the investigator
Second- or third-degree atrioventricular block during screening for eligibility
History of asthma or severe chronic obstructive pulmonary disease
Kidney disease 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

PCI — percutaneous coronary interventions

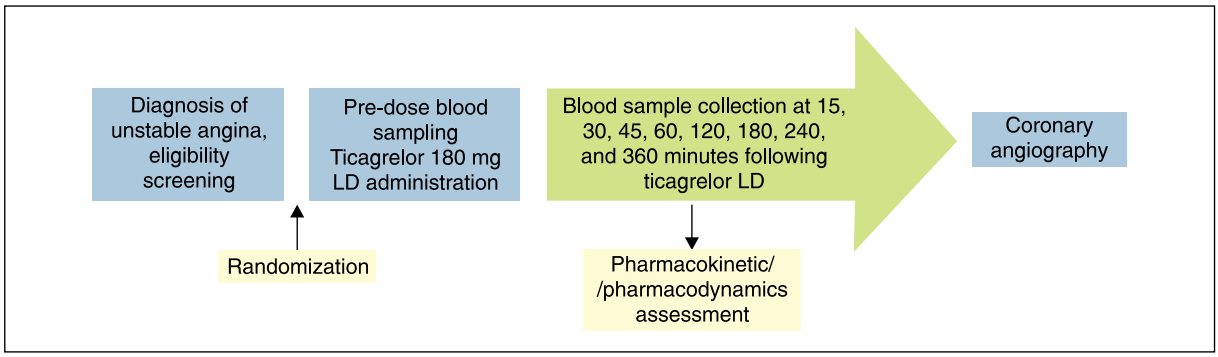

Figure 1. Diagram presenting patient's flow through the study; LD — loading dose

Table 2. List of study endpoints

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

— patients treated with a combination of crushed ticagrelor and morphine (5 mg administered intravenously) and
— patients treated with a combination of crushed ticagrelor followed by morphine (5 mg administered intravenously) and metoclopramide (10 mg administered intravenously).

After the randomization, blood sample collection (time point 0) is planned. Immediately after, a ticagrelor loading dose (LD) will be administered. The schematic diagram of the study is presented in Figure 1.

Endpoints

The time for ticagrelor and its active metabolite AR-C124900XX to reach maximum plasma concentration within time frame of six hours after administration of ticagrelor LD (t_{max}) was determined as the primary outcome of the study.

The study secondary outcomes comprise ticagrelor and AR-C124900XX maximum plasma concentration, area under the plasma concentration-time curve for ticagrelor and AR-C124900XX (AUC 0–6 hours), and platelet reactivity assessed with Multiple Electrode Aggregometry (MEA) measured with a Multiplate Analyzer directly before ticagrelor LD and within a time frame of six hours following ticagrelor LD. The complete list of the study outcomes is presented in Table 2.

Pharmacokinetics and pharmacodynamics

Pharmacokinetic and pharmacodynamic properties of ticagrelor and its active metabolite will be evaluated for all patients enrolled in the study. Pharmacokinetic assessment will be performed by the workers of the Department of Medicinal Chemistry, Nicolaus Copernicus University, Ludwik Rydygier Collegium Medicum in Bydgoszcz using the Shimadzu UPLC Nexera X2 system consisting of LC-30AD pumps, SIL-30AC Autosampler, CTO-20AC column oven, FCV-20-AH2 valve unit, and DGU-20A5R degasser coupled with a Shimadzu 8030 ESI-triple quadrupole mass spectrometer.

Platelet activity will be investigated by blinded researchers in the internal laboratory of the Department of Cardiology using Multiple Electrode Aggregometry (MEA; the Multiplate Analyzer, Roche Diagnostics International Ltd, Rotkreuz, Switzerland). The methods of both pharmacokinetic and pharmacodynamic assessment have been described previously [10, 16].

Blood sample collection

Blood sample collection will be scheduled directly before the administration of ticagrelor LD and 15, 30, 45, 60, 120, 180, 240, and 360 minutes after the LD. The process of blood collection will be performed by the Cardiology Department nurses and supervised by

a physician responsible for each patient's recruitment. An intravenous catheter will be used to reduce the patient's inconvenience associated with blood collection.

Safety of the trial

Only patients diagnosed with unstable angina pectoris scoring less than 140 points in GRACE score (low or intermediate mortality risk) will be enrolled in the study. All participants will be administered standard medications recommended by the ESC guidelines for ACS management, which include 300 mg aspirin loading dose, statins, beta-blockers, angiotensin converting enzyme inhibitors, or angiotensin II receptor inhibitors. The patient's participation in the study will be immediately terminated in the case of any medical conditions requiring urgent coronary angiography. All study participants will be administered ticagrelor maintenance dose of 90 mg twice daily throughout the hospitalisation. Treatment with ticagrelor after discharge will be recommended to each patient at the end of the hospitalisation period. However, a switch to clopidogrel for patients unable to continue therapy with ticagrelor (especially due to economic reasons) will be possible before discharge. These patients will receive a clopidogrel LD of 600 mg.

A single low dose of morphine will be administered intravenously directly after provision of informed consent by each study participant. In the case of any adverse events that may be associated with the use of morphine, an opioid antagonist, naloxone, will be administered to reverse all morphine effects.

Discussion

The current study is, to our knowledge, the first one to provide data on the influence of metoclopramide in patients with ACS, who have received intravenous opioid analgesia. It is expected to contribute to the development of contemporary knowledge on the treatment of patients presenting with ACS, and should enable clinicians to implement strategies of quick platelet inhibition.

The study status

The study was registered in clinicaltrials.gov with the identifier NCT02939235 and it is currently recruiting participants.

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