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The influence of naloxone 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

Rapid platelet inhibition plays pivotal role in contemporary treatment of patients presenting with acute coronary syndromes. Morphine, the most commonly used analgesic has been proven to impair both absorption and onset of action of P2Y12 receptor inhibitors, which can be described as "the morphine effect". Most negative effects of morphine are caused by its undesirable influence on gastrointestinal tract. We hypothesized that naloxone, widely administered intravenous opioid reversing drug, may turn out to be beneficial if given orally in acute coronary syndrome patients previously treated with morphine. Therefore, a phase IV, randomized pilot study was designed so as to evaluate the impact of naloxone administration on pharmacokinetics and pharmacodynamics of P2Y12 inhibitor, ticagrelor in unstable angina patients. A group of 30 consecutive unstable angina patients treated with ticagrelor and morphine will be randomized in a 1:1 ratio into the study arms. To the best of our knowledge, no such approaches to overcome negative influence of morphine in acute coronary syndrome patients have been described in literature so far.

Key words: ticagrelor, morphine, naloxone, pharmacokinetic, pharmacodynamics

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Introduction

Contemporary pharmacological treatment of acute coronary syndromes (ACS) is based on rapid platelet inhibition. According to the latest European Society of Cardiology (ESC) Guidelines for the management of ACS dual antiplatelet therapy with aspirin and a potent P2Y12 receptor inhibitor, preferably ticagrelor, is a recommended approach. Administration of prasugrel is limited to patients whose coronary angiography has been completed and constitutes a strong indication for coronary angioplasty [1]

Throughout the years, patients presenting with symptoms of ACS have been administered morphine as the first line treatment of pain. Pain alleviation is vital not only for humanitarian reasons, but also because of the association of pain with the sympathetic activation leading to vasospasm and increasing the ischemic burden to the heart [2, 3].

Opioid drugs exert their effect through interaction with 3 types of transmembrane G-protein-coupled opioid receptors: μ, δ and κ. The analgetic effect of opioids is mainly attributed to interaction with μ opioid receptors in the central nervous system. Activation of opioid receptors located in smooth muscles and terminal portions of the peripheral sympathetic and sensory nerves of the gastro-intestinal tract depresses gastrointestinal motility and secretion through inhibition of neuronal release of acetylcholine and VASP [5]. Opioid drugs also enhance fluid and electrolyte absorption, mainly through activation of the μ and δ opioid receptors [5]. As a consequence, side-effects such as nausea, vomiting, prolonged gastrointestinal passage, constipation and abdominal discomfort are evoked.

The latest ESC guidelines for the management of patients presenting with ST-segment elevation myocardial infarction (STEMI) lowered the class of recommendation for morphine administration as its negative influence on the pharmacokinetics and pharmacodynamics of ticagrelor has recently been discovered [6, 7]. Morphine has been found to intensify the muscle tone of the gastrointestinal tract, especially the sphincters, which inhibits gastric emptying and weakens intestinal peristalsis, which in turn may lead to the impairment of intestinal absorption and thus to the decrease of peak plasma levels of oral medications [8, 11]. The described phenomenon, which can be called "the morphine effect" is particularly undesirable in patients treated for STEMI, as this population requires immediate platelet inhibition to increase the chance of successful therapy [12–14].

Optimal methods of overcoming "the morphine effect" are yet to be discovered. Several approaches have already been described in literature. These methods include crushing the tablets of P2Y12 receptor inhibitor, which can be useful due to the acceleration of platelets inhibition as a consequence of faster drug absorption or co-administration of prokinetic drug, e.g. metoclopramide so as to speed up the antiplatelet agent absorption [15–18].

The aim of our study is to evaluate the influence of naloxone on the pharmakodynamics and pharmakokinetics of ticagrelor in patients with unstable angina (UA), pretreated with morphine. According to the design of the study, the participants will additionally receive naloxone – a selective opioid receptor antagonist [19], capable of reversing the actions and effects of opioids and commonly used in a variety of clinical scenarios such as:opioid action reversal in opioid intoxication orduring anaesthesia, opioid substitution therapy in opioid addiction and reversal of neonatal respiratory center depression secondary to opioid administration to the mother. In opioid-naive patients, naloxone exerts no significant pharmacological effects. The usual route of administration of naloxone is parenteral. When administered orally or sublingually, naloxone is subjected to very intensive first pass metabolism, resulting in final bioavailability of as little as 2-3%, making its plasmatic concentration barelly detectable [20]. There are literature reports on successful oral administration of naloxone forsevere opioid-related constipation in patients with neoplasmatic diseases, without compromising the analgetic effect of opioids [2, 3, 21, 22], due to local inhibition of intestinal wall opioid receptors [19].

Methods

The study was designed as a phase IV, single-center, randomized, investigator-initiated, parallel-group, open-label, interventional trial. The study protocol was approved by the Ethics Committee of Nicolaus Copernicus University in Toruń, Ludwik Rydygier Collegium Medicum in Bydgoszcz (approval number KB 339/2016). The investigation site will be the Department of Cardiology, Antoni Jurasz University Hospital No. 1 in Bydgoszcz, Poland.

This study was designed to evaluate the impact of naloxone administration on the pharmacodynamics and pharmacokinetics of ticagrelor and its active metabolite AR-C124900XX in patients with UA pectoris who received opioid analgesic in the initial phase of treatment. All enrolled participants will be assigned randomly in a 1:1 ratio to one of the following 2 groups: 1) a group receiving a combination of 180 mg of crushed ticagrelor administered orally followed by intravenous administration of 5 mg of morphine or 2) a group treated with 180 mg of crushed ticagrelor administered orally followed by intravenous administration of 5 mg of morphine and oral administration of 1 mg of naloxone (Figure 1).

Provision of informed consent is mandatory to participate in the study. The main inclusion criterion will be the diagnosis of UA pectoris with a mortality risk of < 140 points according to the GRACE Score. Other inclusion criteria comprise men or non-pregnant women aged 18–80 who have given their informed consent to undergo coronary angiography and percutaneous coronary intervention if required. The main exclusion criteria include recent treatment with any P2Y12 receptor inhibitor, anticoagulants, opioid receptor agonists or potent CYP3A4 inhibitors within 14 days preceding screening, active bleeding, current treatment for malignancy, coagulation disorders, past intracranial hemorrhage, gastrointestinal hemorrhage within 30 days preceding screening, respiratory failure, thrombocytopenia below 100.000/IU or anemia (hemoglobin concentration below 10 g/dL). Also, known hypersensitivity to the administered substances is a disqualifying factor. A complete list of inclusion and exclusion criteria is presented in Table 1.

Sample size calculation

Based on our previous study evaluating the impact of metoclopramide administration on pharmacokinetics (PK) and pharmacodynamics (PD) of ticagrelor and its active metabolite in patients with UA, we assumed that a group of 15 participants in each study arm should provide sufficient data for further analysis [17, 18, 23].

Endpoints

The primary endpoint is the time needed to achieve the maximum plasma concentration of ticagrelor and its active metabolite AR-C124900XX. The secondary

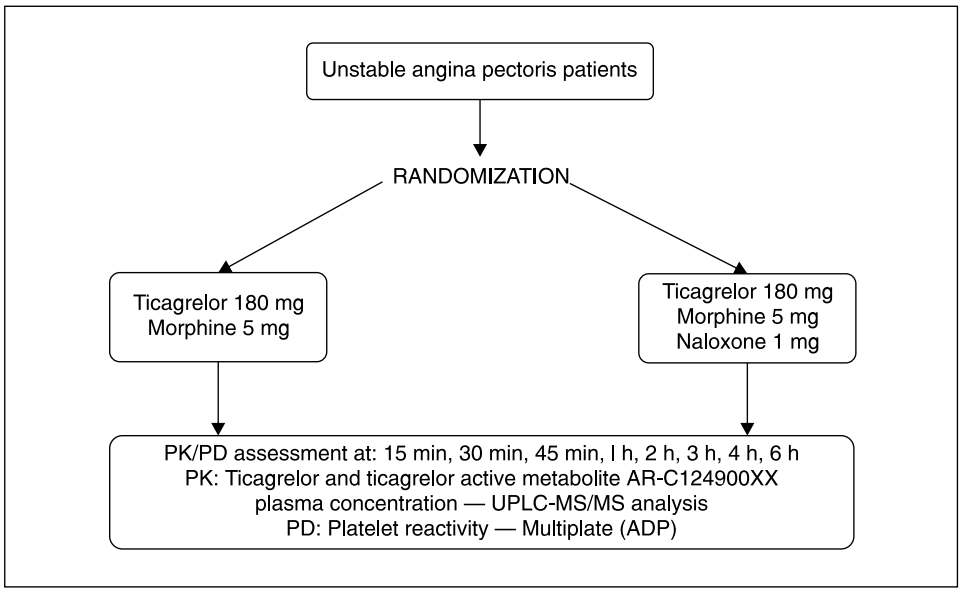

Figure 1. Trial flowchart. PD - pharmacodynamic PK – pharmacokinetic

Table 1. A complete list of inclusion and exclusion criteria for participation 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 enrollment
– 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 hemorrhage
– Recent gastrointestinal bleeding (within 30 days)
– History of coagulation disorders
– Platelet count less than < 100 x 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)
– 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

Table 2. A complete list of study endpoints; AUC – area under the plasma concentraton-time curve of ticagrelor; MEA-multiplate electrode aggregometry

Primary endpoint of the study
— Time to maximum concentration (tmax) for ticagrelor and AR-C124900XX [Time frame: 6 hours]
Secondary endpoints of the study
— 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 MEA [Time frame: pre-dose and 30 min, 1, 2, 3, 4, 6 hours post dose

endpoints include ticagrelor and AR-C124900XX maximum plasma concentration, area under the plasma concentration-time curve (AUC) 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 the time frame of six hours following tikagrelor loading dose (LD). The summary of all study endpoints is presented in Table 2.

The blood sample collection as well as pharmacokinetic and pharmacodynamics assessment have been previously described [7, 17, 18, 24].

Safety assessment

Only patients with low or intermediate risk of mortality defined as less than 140 points in the GRACE Score will be enrolled in the study. The subjects will be treated with a set of standard medications according to the ESC guidelines for the treatment of ACS, including dual anti-platelet therapy, ACE-inhibitor, beta-blocker and statin. When mandated by clinical deterioration requiring urgent coronary angiography, patients will be excluded from further participation in the study and will be immediately transported directly to cathlab. Morphine will be given in a small, single dose after informing the patient about potential consequences associated with treatment with opioids and after acquisition of informed consent from the patient. In case of occurrence of adverse effects after morphine administration, morphine reversing agent, i.e. intravenous naloxone will be given.

Discussion

According to our knowledge, the study is the first attempt to evaluate the influence of naloxone co-administration on the absorption and antiplatelet action of ticagrelor in patients with UA pectoris who received morphine. We hope that the results of our research will broaden the knowledge regarding optimization of ACS treatment and will lead to the development of more effective and safer therapeutic approaches for patients presenting with myocardial infarction.

The study status

The study is currently recruiting participants. It has been registered in clinicaltrials.gov under the identification number NCT02939248.

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Conflict of interest

All authors declare no conflict of interest.

List of abbreviations:

ACS — acute coronary syndromes
AUC — area under the plasma concentraton-time curve of ticagrelor
ECS — European Society of Cardiology
LD — loading dose
MEA — multiplate electrode aggregometry
PD — pharmacodynamic
PK — pharmacokinetic
STEMI — ST-segment elevation myocardial infarction
UA – unstable angina

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