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ABSTRACT

Introduction The unfavourable influence of morphine on the pharmacokinetics of ticagrelor resulting in weaker and retarded antiplatelet effect in patients with acute coronary syndrome (ACS) has been previously shown. Replacing morphine with methoxyflurane, a potent, non-opioid analgesic agent, that does not weaken or delay the effect of antiplatelet agents may improve the clinical efficacy of treatment of patients with ACS.

Methods The ANEMON-SIRIO 3 study was designed as a multicentre, open-label, phase II, randomised clinical trial aimed to test the analgesic efficacy and safety of methoxyflurane in patients with ACS. The study population will comprise patients with ST-elevation myocardial infarction or non-ST-elevation ACS admitted to the study centres with typical chest pain requiring analgesic treatment. Before percutaneous coronary intervention (PCI) for the patients with index ACS will be randomly assigned in 1:1 ratio to receive methoxyflurane administered by inhalation, or to obtain morphine administered intravenously. Analgesic treatment will be followed by 300 mg loading dose of aspirin and 180 mg loading dose of ticagrelor. Patients will be assessed with regard to pain intensity according to the Numeric Pain Rating Scale at baseline, 3 min after study drug administration and immediately after PCI. Moreover, patients will be actively monitored with regard to the occurrence of side effects of evaluated therapies, as well as adverse events that may be related to insufficient platelet inhibition (no-reflow phenomenon assessed immediately after PCI, administration of GPIIb/IIIa inhibitors during PCI, acute stent thrombosis).

Ethics and dissemination The study will be conducted in six Polish clinical centres from the beginning of in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki

Strengths and limitations of this study

- The ANEMON-SIRIO 3 study is designed as a multicentre, open-label, phase II, randomised clinical trial.
- This is the first study aimed to test analgesic efficacy and safety of methoxyflurane in patients with acute coronary syndrome.
- The trial is designed to compare methoxyflurane with morphine which is current analgesic standard of care for chest pain in acute coronary syndromes.
- The study is not powered for the evaluation of Major Adverse Cardiovascular Events (MACE).
- The open label design of the study is burdened with possible evaluation bias of analgesic effect of compared agents.

declaration and its later amendments or comparable ethical standards.

Trial registration details ClinicalTrials.gov, NCT04476173.

INTRODUCTION

Platelet activation plays a pivotal role in the pathophysiology of acute coronary syndromes (ACS). Pharmacological platelet inhibition with P2Y₁₂ receptor antagonists and aspirin, together with percutaneous coronary intervention (PCI) are the cornerstone of treatment of patients with ACS.^{1–8}

Chest pain and anxiety are both associated with sympathetic activation, which increases workload of the heart. Relieving of these symptoms in acute myocardial infarction

(AMI) is expected to improve the balance between the demand for oxygen and its supply. Morphine, apart from its analgesic effects, also alleviates the work of breathing and reduces anxiety. However, despite its favourable analgesic and sedative actions, morphine also exerts adverse effects, which include vomiting and reduction of gastrointestinal motility. These side effects affect the intestinal absorption of oral drugs co-administered with morphine.^{9 10} Previously performed randomised studies revealed unfavourable influence of morphine on the pharmacokinetics of ticagrelor resulting in weaker and retarded antiplatelet effect.^{11–16} Similar effect was observed for clopidogrel^{17 18} and prasugrel,^{17 19 20} but not for aspirin.⁹ Unfortunately, different tested strategies failed to overcome the ‘morphine effect’.^{21–23} Therefore, replacing morphine with another highly effective non-opioid analgesic that does not weaken and does not delay the effect of antiplatelet agents may improve the clinical efficacy of treatment of patients with AMI. An alternative analgesic treatment strategy in patients with ST-elevation myocardial infarction (STEMI) treated with ticagrelor was tested in the ON-TIME 3 trial. Intravenous acetaminophen in comparison with intravenous fentanyl was equally effective in pain relief, however expected difference in platelet reactivity was not significant despite significantly higher ticagrelor plasma concentrations in the intravenous acetaminophen arm.²⁴

Methoxyflurane was shown to be effective and well tolerated for the management of acute traumatic pain with a rapid onset of analgesia. This volatile, non-opioid analgesic agent is self-administered with a hand-held inhaler.^{25 26} As it does not affect the μ -opioid receptors, which inhibit propulsive motility and secretion of the gastrointestinal tract, methoxyflurane is not expected to decrease or delay absorption or effects of orally administered drugs, including P2Y12 inhibitors, as well as to exert any other negative impact in patients with ACS.

However analgesic efficacy and safety of methoxyflurane have never been tested in this clinical setting. The concept to apply methoxyflurane in patients with ACS is supported by recently published results of the AVOID study.²⁷ The reported incidence of no-reflow phenomenon after PCI in patients with STEMI was higher in the high-dose compared with low-dose opioid group. Moreover, higher doses of opioids were associated with greater infarct size.²⁷

METHODS

Study design and population

The ANEMON-SIRIO 3 study was designed as a multicentre, open-label, phase II, randomised clinical trial. Six Polish clinical centres are expected to participate in the trial. The enrolment to the study is scheduled from 1 September 2020 to 31 May 2021. The study population will comprise patients consecutively admitted to the study centres due to ACS with typical chest pain requiring analgesic treatment. Patients aged from 18 to 80 years with STEMI or very high

risk non-ST-elevation ACS (NSTEMI-ACS) with recurrent/refractory chest pain requiring immediate invasive treatment are eligible to participate in the study. The diagnosis of STEMI and non-STEMI will be made according to the Fourth Universal Definition of Myocardial Infarction,²⁸ and unstable angina (UA) will be diagnosed according to the European Society of Cardiology (ESC) guidelines for the management of NSTEMI-ACS.²⁹ The following exclusion criteria were defined: any previously administered analgesic medication for the index ACS, pregnancy, manifest infection or inflammatory state, cardiogenic shock during screening for eligibility, respiratory failure, heart failure (NYHA (New York Heart Association) class III or IV during screening for eligibility), uncontrolled hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure >100 mm Hg).

Ethics and dissemination

The study will be conducted in accordance with the principles contained in the Declaration of Helsinki. The ANEMON-SIRIO 3 study protocol and the template informed consent forms received approval from the Bioethics Committee (BC) of the Collegium Medicum, Nicolaus Copernicus University in Toruń (study approval reference number KB 38/2020). The investigators will report the progress and safety of the study to the BC and to the Data Safety and Monitoring Board every 2 months. The final report (manuscript for publication) of the study results will be prepared within 1 month after study completion. The report will be available at ClinicalTrials.gov Identifier: NCT04476173.

Treatment protocol and concomitant medications

Patients with initial diagnosis of STEMI or NSTEMI-ACS will be screened for eligibility for the study. The informed consent will be obtained in the setting of acute pain therefore the abbreviated information regarding the study and investigated treatment will be provided verbally. The patient will receive full written information, and will sign the consent with the abbreviated and full version of the information. Before PCI for the index ACS, after obtaining informed consent patients will be enrolled and randomly assigned with a secure online system in 1:1 ratio to one of two study arms. The study design is depicted in [figure 1](#).

Patients in the intervention arm will receive methoxyflurane administered by inhalation (3 mg vial), whereas those in the control arm will obtain 5 mg of morphine administered intravenously. Efficacy of analgesics in both arms will be evaluated 3 min after initiation of treatment (study endpoint). The Numeric Pain Rating Scale (NPRS) will be applied for pain intensity assessment. Improvement is defined as reduction of pain intensity by at least 2 NPRS points. The pathways of analgesic treatment in both arms are shown on [figure 2A,B](#). According to the study protocol, unbearable chest pain persisting regardless of the administered analgesics and performed coronary revascularisation, will be considered a strong indication for a crossover, which will be left to the discretion of the investigator.

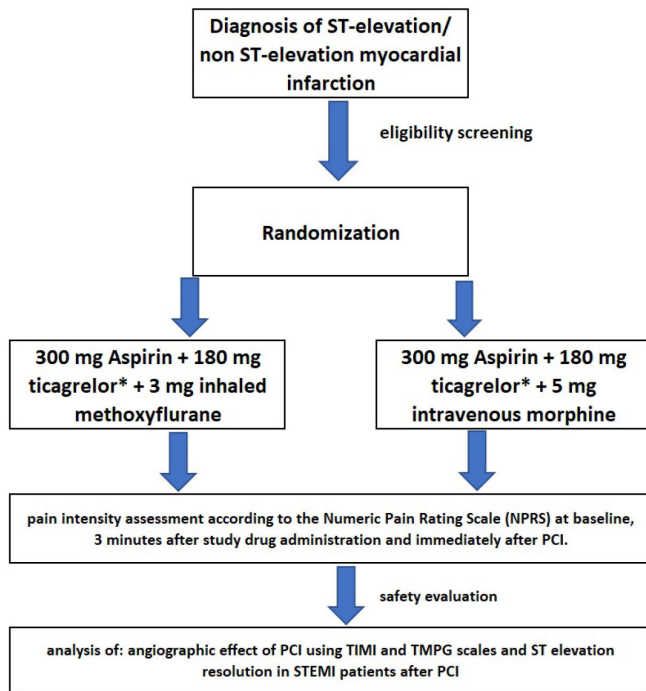


Figure 1 The study design. *Patients previously loaded with clopidogrel will be reloaded with ticagrelor after randomisation. PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction; TMPG, TIMI Myocardial Perfusion Grade.

Analgesic treatment in all enrolled subjects will be followed by 300 mg loading dose of aspirin and 180 mg loading dose of ticagrelor. Subjects loaded with clopidogrel or prasugrel before the study enrolment will be re-loaded with 180 mg ticagrelor in line with the European Society of Cardiology (ESC) recommendations.⁷ All patients during their participation in the study, will be treated according to the ESC guidelines, including primary PCI.^{7,8} Patients will be observed up to 24 hours after PCI. During their participation in the study, all patients will be assessed with regard to pain intensity according to the NPRS at baseline, 3 min after study drug administration and immediately after PCI. Moreover, patients will be actively monitored with regard to the occurrence of side effects of evaluated therapies, as well as adverse events that may be related to insufficient platelet inhibition (no-reflow phenomenon assessed immediately after PCI, administration of GPIIb/IIIa inhibitors during PCI, acute stent thrombosis). Platelet reactivity will be assessed with VerifyNow System 2 hours after loading with P2Y₁₂ receptor inhibitor. Clinical research showed that nephrotoxicity was a dose-related complication caused by fluoride ions produced by O-demethylation of methoxyflurane. It was observed at high anaesthetic doses, but not reported with low analgesic doses.³⁰ Therefore, renal function will not be assessed before enrolment into the study. Nevertheless, renal function

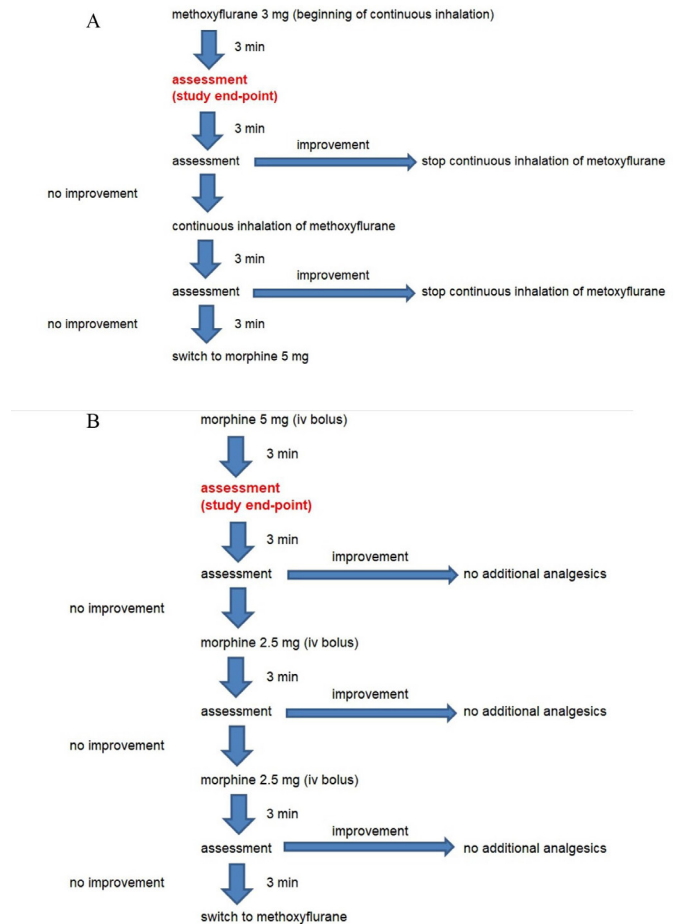


Figure 2 (A) The pathway of analgesic treatment in methoxyflurane arm. (B) The pathway of analgesic treatment in morphine arm. iv, intravenous.

will be monitored after coronary intervention due to possible contrast-induced kidney injury.³¹

Study endpoints

Two co-primary endpoints are defined as the measure of pain intensity according to the NPRS 3 min after drug administration and immediately after PCI in relation to pain intensity assessed before drug administration.

The following secondary endpoints are established: adverse effects of evaluated therapies (nausea, vomiting, dry mouth, respiratory failure - need for intubation, headache, dizziness, drowsiness, loss of consciousness, death), need for GPIIb/IIIa inhibitor administration during PCI due to large intracoronary thrombus. Additionally, a central analysis of: (1) angiographic effect of PCI using TIMI and TMPG scales and (2) ST elevation resolution in patients with STEMI after PCI (with a 70% resolution cut-off) will be done.

Determination of sample size

We assume that inclusion of 200 patients (1:1 ratio between intervention and control arms) would be sufficient to show non-inferiority of methoxyflurane as compared with morphine with regard to analgesic effect in patients with ACS with a two-sided alpha value of 0.05 and at least 80% power. Since there is no reference study, we decided to

perform an internal pilot phase of the study including the first 100 patients (50 patients for each arm) for estimating the final sample size.

Patient and public involvement

No patient involved.

Statistical analysis

The continuous variables in the two arms will be compared with parametric tests (Student's t-test) or non-parametric tests (Mann-Whitney test), if the assumptions for parametric analysis are not satisfied. The categorical data will be analysed with χ^2 test and the Fisher's exact test. Event-free survival analysis will be performed by the Kaplan-Meier method with log-rank test for group comparison. Tests results yielding $p < 0.05$ will be considered as statistically significant.

DISCUSSION

The antiplatelet drugs administration is of vast importance, especially in the initial phase of ACS treatment.^{3 4 32} Results of the PLATO trial have shown that the therapy with ticagrelor, a novel potent platelet P2Y₁₂ receptor inhibitor, reduces all-cause mortality and the rates of cardiovascular events compared with clopidogrel in patients with ACS, including STEMI.⁵ The observed superiority of ticagrelor over clopidogrel in decreasing ischaemic event rate in patients with ACS has been attributed to a fast, potent and uniform pharmacodynamic features.⁶ The ECS recommends ticagrelor (180 mg loading dose, followed by 90 mg two times per day) on top of aspirin in patients with ACS regardless of initial treatment strategy.^{7 8} The same guidelines recommend use of titrated opioid agents, (eg, morphine) as a treatment of choice for pain relief in this clinical setting.⁸ The highly possible impact of morphine—ticagrelor interaction on clinical outcomes in patients with AMI has never been proven.¹⁰ The negative effect of drug–drug interaction can possibly be balanced by an analgesic effect of morphine. Therefore, replacing morphine with another highly effective non-opioid analgesic that does not weaken and does not delay the effect of antiplatelet agents may improve the clinical efficacy of treatment of patients with ACS.

Study limitations

It should be highlighted that the ANEMON-SIRIO 3 study is not powered for the evaluation of Major Adverse Cardiovascular Events (MACE) or angiographic endpoints. Moreover, the open label design of the study is burdened with possible evaluation bias of analgesic effect of compared agents.

In summary, the aim of the ANEMON-SIRIO 3 study is to evaluate analgesic efficacy and safety of treatment with inhaled methoxyflurane versus intravenously administered morphine for pain relief in patients with ACS treated with PCI.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

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