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ORIGINAL ARTICLE

Comparative effects of fentanyl versus morphine on platelet inhibition induced by ticagrelor in patients with ST-segment elevation myocardial infarction: Full results of the PERSEUS randomized trial

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Abstract

Background: *Morphine reduces absorption and delays action onset of potent oral P2Y$_{12}$ receptor inhibitors in patients with ST-segment elevation myocardial infarction (STEMI). We sought to determine the differential effects of fentanyl compared to morphine on the pharmacodynamics and pharmacokinetics of ticagrelor in STEMI patients undergoing primary percutaneous coronary intervention (PCI).*

Methods: *PERSEUS (NCT02531165) was a prospective, single-center, open-label, randomized controlled study. Patients with STEMI who required analgesia were randomly assigned in a 1:1 ratio to treatment with intravenous fentanyl or morphine after ticagrelor loading dose (LD) administration. The primary endpoint was platelet reactivity at 2 hours after ticagrelor LD assessed by P2Y$_{12}$ reaction units (PRU).*

Results: *The study was prematurely stopped in June 2017 after enrolment of 38 out of 56 planned patients. PRU at 2 hours following ticagrelor LD was 173.3 ± 89.7 in the fentanyl group and 210.3 ± 76.4 in the morphine group (p = 0.179). At 4 hours, PRU was significantly lower among patients treated with fentanyl as compared to those treated with morphine (90.1 ± 97.4 vs. 168.0 ± 72.2; p = 0.011). Maximal plasma concentrations of ticagrelor and its active metabolite AR-C124910XX tended to be delayed and numerically lower among patients treated with morphine compared to fentanyl. Total exposures to ticagrelor and AR-C124910XX within 6 hours after ticagrelor LD were numerically greater among patients treated with fentanyl compared to those treated with morphine.*

Conclusions: *In patients with STEMI undergoing primary PCI, fentanyl did not improve platelet inhibition at 2 hours after ticagrelor pre-treatment compared with morphine. Fentanyl may, however, accelerate ticagrelor absorption and increase platelet inhibition at 4 hours compared to morphine.* (Cardiol J 2022; 29, 4: 591–600)

Key words: fentanyl, pharmacodynamics, pharmacokinetics, ST-segment elevation myocardial infarction, ticagrelor

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Introduction

Dual antiplatelet therapy combining acetylsalicylic acid (ASA) and a $P2Y_{12}$ receptor antagonist is a cornerstone in the pharmacological treatment of patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI)[1]. Early optimal $P2Y_{12}$ receptor inhibition has been shown to improve coronary reperfusion before primary PCI and clinical outcomes compared to a delayed $P2Y_{12}$ inhibition strategy in patients with STEMI [2]. However, platelet inhibitory effects induced by potent oral $P2Y_{12}$ receptor antagonists are delayed in patients with STEMI [3, 4]. Recent pharmacological studies have demonstrated that morphine further reduces absorption, delays onset of action, and decreases antiplatelet effects of oral $P2Y_{12}$ inhibitors among STEMI patients undergoing primary PCI [4–7], which potentially results in an increased risk of stent-related adverse outcomes [8].

Fentanyl is a potent, fast-acting, and effective intravenous synthetic opioid agent [9], which is frequently used for procedural analgesia during cardiac catheterization procedures [10]. Recently, fentanyl has been shown to reduce ticagrelor absorption and delay platelet inhibition compared with placebo in patients with chronic coronary syndrome [11, 12], but the potential influence of fentanyl on ticagrelor absorption and platelet inhibition in patients with acute STEMI remains uncertain. We recently reported the main results for the primary and selected prespecified secondary endpoints from the Platelet Inhibition after Pre-hospital Ticagrelor using Fentanyl compared to Morphine in patients with ST-segment elevation Myocardial Infarction undergoing Primary Percutaneous Coronary Intervention (PERSEUS) randomized trial, which compared fentanyl versus morphine regarding ticagrelor pharmacokinetics and pharmacodynamics among STEMI patients undergoing primary PCI, and demonstrated that fentanyl did not improve platelet inhibition at 2 hours compared with morphine [13]. However, the full results from the PERSEUS trial have not been published to date. Herein, we report baseline demographic and procedural characteristics of the study population, patient self-reported pain scores, complete platelet function results, and prespecified coronary reperfusion outcomes.

Methods

Study design and patient population

PERSEUS was an investigator-initiated, prospective, single-center, open-label, randomized controlled trial. A detailed description of the study rationale and design has been previously published [14]. Briefly, patients with STEMI undergoing primary PCI within 12 hours of symptoms' onset were eligible for inclusion. Key inclusion and exclusion criteria have been reported previously [14]. Patients on chronic $P2Y_{12}$ receptor antagonist or oral anticoagulation therapy, or who received glycoprotein IIb/IIIa inhibitors were excluded. In addition, patients with medical conditions that may adversely affect gastrointestinal absorption and metabolic activation of oral $P2Y_{12}$ receptor inhibitors, including comatose patients or those with cardiogenic shock, were excluded. All patients were pre-treated with ASA (loading dose [LD] 500 mg), ticagrelor (LD 180 mg), and unfractionated heparin (LD 5000 IU or 70–100 IU per kg of body weight) at the time of STEMI diagnosis. Patients requiring analgesia for pain relief (visual analogue scale [VAS] score ≥ 3) were randomly assigned in a 1:1 ratio to treatment with intravenous fentanyl (50–100 μg) or morphine (4–8 mg) using a centralized telephone treatment allocation. Additional doses of fentanyl (25 μg, every 2–5 min) or morphine (2 mg, every 5–15 min) were administrated to achieve adequate analgesia (VAS score < 3). All patients underwent primary PCI according to institutional standards. The choice of vascular access site, periprocedural anticoagulation regimen, and procedural techniques was left to the discretion of the treating physician. After primary PCI, all patients received a maintenance dose of ASA (100 mg daily) indefinitely. A ticagrelor maintenance dose (90 mg twice daily) was initiated 12 hours after the LD and was recommended for at least 12 months. The study protocol complied with the Declaration of Helsinki. The study protocol was approved by the local Ethics Committee at Lausanne University Hospital, Switzerland (Project ID: PB_2016-00291). All enrolled patients provided written informed consent for participation. The trial was registered with ClinicalTrials.gov, identifier NCT02531165.

Pharmacodynamic assessments

Blood samples were collected at baseline and at 1, 2, 4, 6, and 12 hours after ticagrelor LD admin-

istration [13]. Platelet reactivity was determined as P2Y$_{12}$ reaction units (PRU) using the VerifyNow® P2Y$_{12}$ function assay (Accumetrics, Inc., San Diego, California, USA) at 1, 2, 4, 6, and 12 hours, and platelet reactivity index (PRI) using the Vasodilator-Stimulated-phosphoprotein Phosphorylation (VASP) assay (Biocytex, Inc., Marseille, France) at 1, 2, and 4 hours after ticagrelor LD administration [14]. High on-treatment platelet reactivity (HTPR) was defined as PRU ≥ 240 or PRI ≥ 50% [15].

Pharmacokinetic assessments

Plasma concentrations of ticagrelor and its major active metabolite AR-C124910XX were determined by a blinded external laboratory (Covance Laboratories, Indianapolis, Indiana, USA) at 1, 2, 4, 6, and 12 hours after ticagrelor pre-treatment using high-performance liquid chromatography combined with tandem mass spectrometry detection in the negative ion mode after protein precipitation extraction. A detailed description of blood samples collection and preparation has been reported previously [13]. Baseline ticagrelor and AR-C124910XX plasma concentrations were presumed to be zero because subjects on chronic P2Y$_{12}$ receptor inhibitors were excluded. The lower limits of quantification for ticagrelor and AR-C124910XX were 1 ng/mL and 2.5 ng/mL, respectively.

Study endpoints

The primary endpoint was platelet reactivity assessed by PRU at 2 hours after ticagrelor LD administration. Prespecified secondary endpoints include platelet reactivity assessed by PRU at 1, 4, 6, and 12 hours after ticagrelor LD, the proportion of patients with HTPR at 1, 2, 4, 6, and 12 hours after ticagrelor LD, the peak plasma concentration (C$_{max}$) of ticagrelor and AR-C124910XX at 1, 2, 4, 6, and 12 hours after ticagrelor LD, the time to peak plasma concentration (T$_{max}$) for ticagrelor and AR-C124910XX, the area under the plasma concentration-time curve for ticagrelor and AR-C124910XX during the first 6 hours after ticagrelor LD (AUC$_{0-6}$), the proportion of patients with thrombolysis in myocardial infarction (TIMI) grade 3 flow in the infarct-related artery before primary PCI, and the proportion of patients with ≥ 70% ST-segment elevation resolution after primary PCI. Data collection and monitoring have been described previously [14]. Study endpoints were independently adjudicated by a clinical events committee blinded to treatment assignment.

Sample size calculation

At the time of the study design, there was no reference study examining the effects of fentanyl on the pharmacodynamics and pharmacokinetics of P2Y$_{12}$ receptor inhibitors in patients with STEMI treated with primary PCI. Based on the results of previous studies [4–7], we assumed a mean PRU value of 190 at 2 hours after ticagrelor administration in STEMI patients undergoing primary PCI after receiving analgesia with morphine. We presumed that platelet reactivity assessed by PRU at 2 hours after ticagrelor loading dose administration would be lower in patients receiving fentanyl as compared to morphine (PRU 160 ± ± 40; absolute platelet reactivity difference, 30 PRU; relative platelet reactivity difference, 16%) due to differential involvement of μ-opioid receptor sites and responsible regions between fentanyl and morphine, which results in varying effects on gastrointestinal motility and degrees of induced dysmotility [14]. Assuming a two-sided statistical significance level of 0.05 and 95% confidence interval (CI), we calculated that enrolment of a total of 56 patients (28 in both study groups) would provide 80% power to demonstrate a significant difference in PRU values at 2 hours after ticagrelor LD administration between treatment arms.

Statistical analysis

All analyses were performed according to the intention-to-treat principle. The results are presented as percentages for categorical variables and mean ± standard deviation or medians (interquartile range [IQR]) for continuous data with normal and skewed distributions, respectively. Comparisons between categorical data were performed using Fisher's exact test, whereas Student's t-test and the Mann-Whitney test were used for comparisons of continuous and ordinal data, as appropriate. Comparisons between paired samples were performed using paired sample t-test or Wilcoxon sum rank test. Statistical significance was considered for p values < 0.05. All statistical analyses were performed using SPSS software (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5.0 for Windows (GraphPad Software, La Jolla CA, USA).

Results

Between December 18, 2015 and June 22, 2017, 38 patients were included and randomly assigned to treatment with fentanyl (n = 19) or morphine
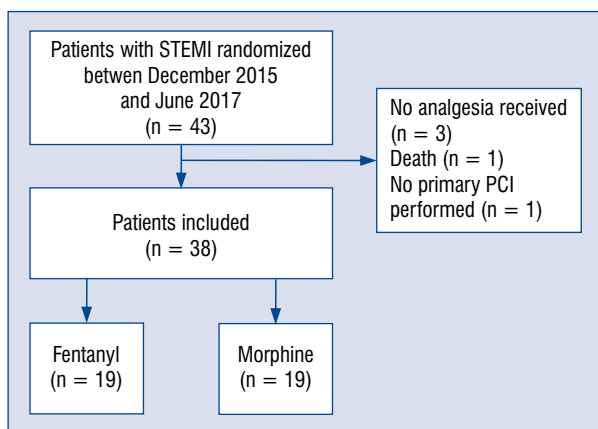
Figure 1. Patient flow chart according to the CONSORT statement; PCI — percutaneous coronary intervention; STEMI — ST-segment elevation myocardial infarction.

(n = 19) (Fig. 1). The study was prematurely stopped due to a slower than anticipated patient enrolment rate after inclusion of 38 (68%) of the 56 patients planned. Patient baseline and procedural characteristics were similar between the two treatment groups (Table 1). Median age was 68.6 ± 13.1 years in the fentanyl group and 65.2 ± 16.2 years in the morphine group (p = 0.46). Median reperfusion delays from STEMI diagnosis to primary PCI and from ticagrelor loading dose administration to primary PCI did not differ between patients treated with fentanyl or morphine. Infarct-related coronary artery characteristics and final myocardial infarct size, as assessed by peak troponin levels, were comparable between the two treatment groups. Finally, mean self-reported VAS pain score was similar in the fentanyl and the morphine groups, both at the time of randomization (4.8 ± 5.5 vs. 6.3 ± 1.7; p = 0.50) and before PCI (2.4 ± 2.6 vs. 1.9 ± 2.3; p = 0.57).

Pharmacodynamic assessment

The primary endpoint, mean PRU at 2 hours after ticagrelor LD, was 173.3 ± 89.7 in patients treated with fentanyl and 201.3 ± 76.4 among those receiving morphine (p = 0.179). Mean PRU values were significantly lower with fentanyl at 4 hours compared with morphine (90.1 ± 97.4 vs. 168.0 ± ± 72.2; p = 0.011). However, the differences in mean PRU values did not significantly differ at 6 hours (79.3 ± 89.1 vs. 122.2 ± 80.3; p = 0.14) and 12 hours (51.3 ± 53.3 vs. 83.3 ± 63.8; p = 0.11) after ticagrelor LD administration between patients treated with fentanyl and those receiving morphine (Table 2). The rates of HTPR were similar throughout the 6 hours after ticagrelor LD administration

between patients treated with fentanyl or morphine (Fig. 2). PRI at 1, 2, and 4 hours after ticagrelor LD administration among patients treated with fentanyl or morphine are reported in Table 2.

Pharmacokinetic assessment

The pharmacokinetic profile of ticagrelor and AR-C124910XX among patients treated with fentanyl or morphine after ticagrelor LD administration are detailed in Table 3. Overall, mean C_{max} for ticagrelor and AR-C124910XX within 12 hours of ticagrelor pre-treatment did not significantly differ between patients treated with fentanyl or morphine (Table 3). Mean C_{max} for the active metabolite AR-C124910XX was, however, significantly lower at 6 hours (154.8 ± 128.5 vs. 74.6 ± 63.4 ng/mL; p = 0.011) among patients treated with fentanyl as compared to those receiving morphine (Table 3). Median T_{max} for ticagrelor (6 h; IQR 4–12 vs. 12 h; IQR 4–12; p = 0.325) and AR-C124910XX (6 h; IQR 4–12 vs. 12 h; IQR 6–12; p = 0.070) were similar among patients treated with fentanyl and morphine (Table 3). Total exposures to ticagrelor (1386 ng × h//mL; IQR 96–2765 vs. 579 ng × h/mL; IQR 74–1108; p = 0.108) and AR-C124910XX (293 ng × h/mL; IQR 17–881 vs. 71 ng × h/mL; IQR 17–225; p = 0.080) within 6 hours of ticagrelor pre-treatment were numerically greater among patients treated with fentanyl versus morphine (Table 3).

Coronary perfusion outcomes

TIMI grade < 3 flow in the infarct-related artery before primary PCI was found in 18 (94.7%) patients in the fentanyl group and in 18 (94.7%) patients in the morphine group (p = 1.00) (Fig. 3). Following ticagrelor LD administration, ST-segment elevation resolution < 70% after primary PCI was observed in 9 (60%) patients in the fentanyl group and in 8 (50%) patients in the morphine group (p = 0.47) (Fig. 3).

Discussion

In the PERSEUS randomized trial, fentanyl did not improve platelet inhibition at 2 hours after ticagrelor LD administration compared to morphine among patients with STEMI undergoing primary PCI. Despite the premature study termination resulting in loss of statistical power, there was consistent pharmacodynamic and pharmacokinetic evidence that fentanyl may be associated with a more favorable ticagrelor absorption profile than morphine. The use of fentanyl in symptomatic patients with STEMI, who were pre-treated with

Table 1. Patient baseline and procedural characteristics.

Characteristics	Fentanyl (n = 19)	Morphine (n = 19)	P
Age [years]	68.6 ± 13.1	65.2 ± 16.2	0.46
Male	13 (68.4%)	14 (73.7%)	0.72
Body mass index [kg/m^2]	26.7 ± 5.7	26.5 ± 3.7	0.93
Hypertension	8 (42.1%)	10 (52.6%)	0.51
Dyslipidemia	7 (36.9%)	8 (42.1%)	0.74
Diabetes mellitus	3 (15.8%)	3 (15.8%)	1.00
Current smoker	9 (47.4%)	8 (42.1%)	0.74
Prior coronary artery disease	1 (5.3%)	3 (15.7%)	0.29
Prior myocardial infarction	1 (5.3%)	4 (21.1%)	0.15
Prior PCI	0 (0%)	3 (15.7%)	–
Prior CABG	0 (0%)	0 (0%)	–
Prior stroke	0 (0%)	0 (0%)	–
Peripheral arterial disease	1 (5.3%)	2 (10.5%)	0.55
Chronic kidney disease	2 (10.5%)	2 (10.5%)	1.00
Medication at admission:			
Oral anticoagulation	0 (0%)	1 (5.3%)	–
Acetylsalicylic acid	4 (21.1%)	7 (36.8%)	0.28
Statin	5 (26.3%)	7 (36.8%)	0.48
Beta-blocker	2 (10.5%)	4 (21.1%)	0.37
ARB/ACE inhibitor	4 (21.1%)	4 (21.1%)	1.00
Vital signs:			
Systolic BP [mmHg]	128.9 ± 27.1	121.1 ± 21.2	0.33
Diastolic BP [mmHg]	73.0 ± 15.2	70.7 ± 11.3	0.60
Heart rate [bpm]	77.5 ± 20.3	75.9 ± 12.6	0.77
STEMI diagnosis to primary PCI time [min] (median, IQR)	108.0 (24.2)	105.0 (22.4)	0.74
Ticagrelor loading dose to primary PCI time [min] (median, IQR)	72.5 (32.4)	84.5 (20.3)	0.17
Cardiogenic shock	2 (10.5%)	1 (5.3%)	0.52
Infarct-related coronary vessel:			
Left anterior descending artery	7 (36.8%)	8 (42.1%)	0.74
Left circumflex artery	4 (21.1%)	3 (15.8%)	0.67
Right coronary artery	8 (42.1%)	7 (36.8%)	0.74
Other	0 (0%)	1 (5.3%)	–
Peak troponin level [ng/L] (median, IQR)	6719.9 ± 6463.6	6211.4 ± 8934.4	0.84
Visual Analogue Scale score:			
At randomization	4.8 ± 5.5	6.3 ± 1.7	0.50
Before PCI	2.4 ± 2.6	1.9 ± 2.3	0.57

Values are mean ± standard deviation, n (%), or median [interquartile range (IQR)]. ACE — angiotensin converting enzyme; ARB — angiotensin receptor blockers; BP — blood pressure; CABG — coronary artery bypass grafting; PCI — percutaneous coronary intervention; STEMI — ST-segment elevation myocardial infarction

ticagrelor, may accelerate ticagrelor absorption, and result in significantly increased platelet inhibition at 4 hours compared to morphine. To our knowledge, PERSEUS represents the first direct randomized comparison between fentanyl and morphine with regards to the pharmacodynamic and pharmacokinetic response to ticagrelor in STEMI patients requiring analgesia.

Rapid-onset and effective platelet P2Y$_{12}$ receptor inhibition represents the mainstay of pharmacological treatment in patients with STEMI undergoing primary PCI [1]. However, antiplatelet

Table 2. Pharmacodynamic assessment with $P2Y_{12}$ reaction units and platelet reactivity index after ticagrelor loading dose (LD) administration in patients treated with fentanyl versus morphine.

	Fentanyl (n = 19)	Morphine (n = 19)	P
$P2Y_{12}$ reaction units			
At baseline	188.89 ± 47.51	205.00 ± 49.16	0.331
At 1 hour post LD	187.84 ± 87.56	202.47 ± 66.87	0.566
At 2 hours post LD	173.26 ± 89.69	201.32 ± 76.41	0.179
At 4 hours post LD	90.11 ± 97.42	168.00 ± 72.24	0.011
At 6 hours post LD	79.33 ± 89.10	122.17 ± 80.34	0.139
At 12 hours post LD	51.33 ± 53.29	83.33 ± 63.81	0.112
Platelet reactivity index			
At 1 hour post LD	56.52 ± 26.93	76.35 ± 16.39	0.013
At 2 hours post LD	54.27 ± 27.45	64.82 ± 24.28	0.237
At 4 hours post LD	34.38 ± 27.42	52.12 ± 30.60	0.086

Values are mean ± standard deviation
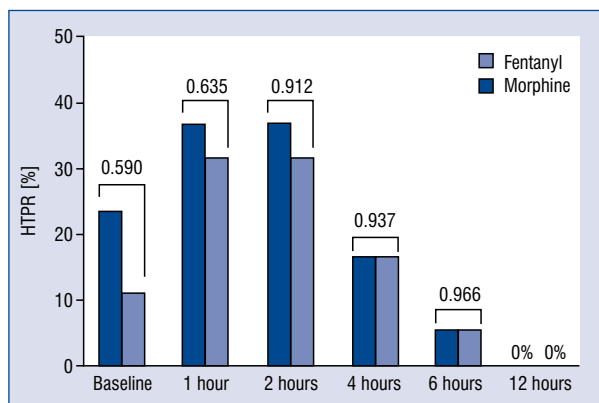
Figure 2. High on-treatment platelet reactivity rates following ticagrelor loading dose administration in patients treated with fentanyl versus morphine; HTPR — high on-treatment platelet reactivity as assessed by the Verify-Now $P2Y_{12}$ assay. Histograms represent rates.

inhibitory effects induced by potent oral $P2Y_{12}$ receptor antagonists are substantially delayed in STEMI patients [3, 4] owing to impaired gastrointestinal absorption [16]. The results of the present analysis are consistent with previous pharmacological studies indicating that intravenous opioid agents delay the absorption and the onset of action of orally administered $P2Y_{12}$ receptor antagonists in patients undergoing primary PCI for STEMI, which results in reduced plasma concentrations, delayed antiplatelet effects, and increased platelet reactivity of oral $P2Y_{12}$ receptor inhibitors [3, 7]. In the IMPRESSION randomized trial [7], morphine co-administration with ticagrelor was associated with reduced total exposure to ticagrelor and its active metabolite, which resulted in delayed and attenuated maximal plasma concentrations of ticagrelor compared to placebo among patients with acute myocardial infarction. The adverse pharmacological effects of morphine on oral $P2Y_{12}$ receptor antagonists are likely caused by the inhibition of normal muscular activity of the gastrointestinal tract in patients with STEMI [17, 18]. Our findings confirm that the delayed and reduced antiplatelet effects of potent oral $P2Y_{12}$ receptor inhibitors in STEMI patients treated with intravenous opioid agents are mainly attributed to an altered pharmacokinetic profile, which reduces total exposure to oral $P2Y_{12}$ receptor inhibitors within the first hours after LD administration.

The clinical implications of the pharmacological interaction between μ-opioid receptor agonists and $P2Y_{12}$ receptor inhibitors in patients with acute coronary syndrome (ACS) remain controversial. In the FAST-MI registry, in-hospital and 1-year rates of major adverse ischemic outcomes were similar between STEMI patients who received, as compared to those who did not receive, prehospital morphine, but the risk of myocardial re-infarction during admission was significantly higher among patients pretreated with morphine [19]. Conversely, morphine was associated with higher risk-adjusted in-hospital and 30-day rates of ischemic events among patients with non ST-elevation ACS pretreated with clopidogrel in the EARLY ACS trial [20], thus disclosing the need for future research on alternatives to morphine in ACS patients requiring analgesia. Different strategies have been proposed

Table 3. Pharmacokinetic assessment of ticagrelor and AR-C124910XX after ticagrelor loading dose (LD) administration in patients treated with fentanyl versus morphine.

	Fentanyl (n = 19)	Morphine (n = 19)	P
Ticagrelor			
T$_{max}$ [h]	6 (4–12)	12 (4–12)	0.325
C$_{max}$ [ng/mL]			0.202
at 1 hour post LD	184.8 ± 361.6	32.3 ± 56.7	0.078
at 2 hours post LD	245.1 ± 390.7	107.6 ± 246.7	0.203
at 4 hours post LD	425.3 ± 450.4	294.0 ± 551.2	0.439
at 6 hours post LD	550.7 ± 506.6	327.1 ± 372.1	0.489
at 12 hours post LD	425.1 ± 423.6	371.1 ± 295.7	0.666
AUC$_{0-6}$ [ng × h/mL]	1386 (96–2765)	579 (74–1108)	0.108
AR-C124910XX			
T$_{max}$ [h]	6 (4–12)	12 (6–12)	0.070
C$_{max}$ [ng/mL]			0.308
at 1 hour post LD	22.7 ± 44.9	24.5 ± 13.4	0.095
at 2 hours post LD	42.7 ± 72.8	27.0 ± 45.6	0.129
at 4 hours post LD	99.9 ± 112.9	66.9 ± 68.3	0.083
at 6 hours post LD	154.8 ± 128.5	74.6 ± 63.4	0.011
at 12 hours post LD	141.1 ± 125.1	121.0 ± 104.1	0.504
AUC$_{0-6}$ [ng × h/mL]	293 (17–881)	71 (17–225)	0.080

Values are mean ± standard deviation or median [interquartile range (IQR)]. AUC$_{0-6}$ — area under the plasma concentration-time curve at 6 hours after ticagrelor loading dose; C$_{max}$ — peak plasma concentration; T$_{max}$ — time to peak plasma concentration
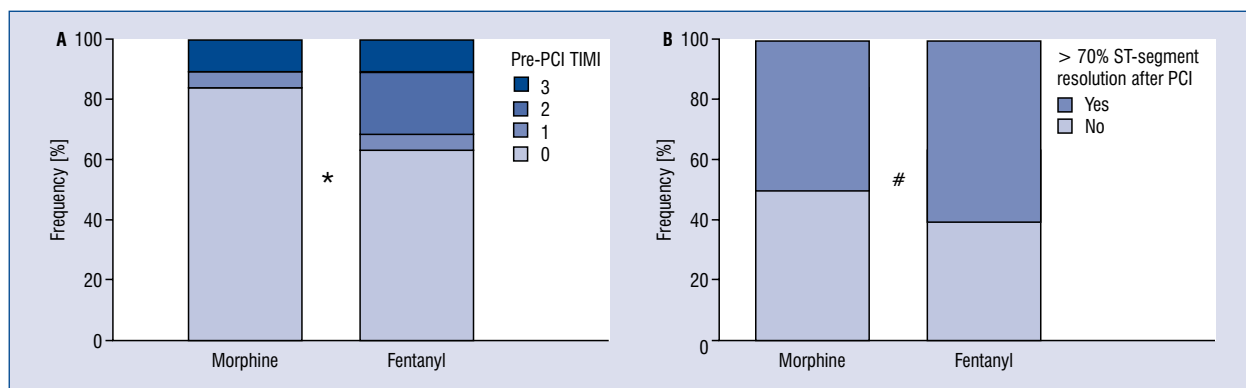
Figure 3. Coronary perfusion outcomes before primary percutaneous coronary intervention (PCI) in patients treated with fentanyl versus morphine. Proportion of patients with thrombolysis in myocardial infarction (TIMI) flow grade 0 to 3 in the infarct-related artery (**A**), and with or without ≥ 70% ST-segment elevation resolution (**B**) before primary PCI; *p-value for comparison of TIMI flow grade 3 between the fentanyl and morphine groups = 0.34; #p-value for comparison of > 70% ST-segment resolution after PCI between the fentanyl and morphine groups = 0.58.

to bridge the initial gap in platelet inhibition and overcome high on-treatment residual platelet reactivity associated with the use of oral P2Y$_{12}$ inhibitors in STEMI patients, including upstream P2Y$_{12}$ receptor antagonist administration [21], escalating P2Y$_{12}$ receptor inhibitor LD regimens [16], intravenous P2Y$_{12}$ receptor antagonists [22], use of glycoprotein IIb/IIIa inhibitors [23], or co-administration of a prokinetic agent [24]. To date, it remained uncertain whether intravenous opioid agents such as fentanyl have similar adverse pharmacological effects on orally administered P2Y$_{12}$ receptor antagonists in patients with STEMI. Recent evidence indicates that μ-opioid receptor

agonists have differential pharmacological profiles and exert their effects by involvement of different μ-opioid receptor sites and varying degrees of gastrointestinal dysmotility [25]. Fentanyl is a potent, fast-acting, and effective intravenous synthetic opioid agent [9], which displays different pharmacological dose-response curves and mitigates gastrointestinal motility inhibition compared to morphine [25], hence theoretically improving the absorption and the bioavailability of orally administered drugs. In the PACIFY trial, fentanyl has been shown to reduce plasma concentration and delay antiplatelet effects of ticagrelor compared with placebo, but the study only included patients undergoing PCI for chronic coronary syndrome [11, 12]. To the best of our knowledge, PERSEUS is the first head-to-head randomized trial designed to specifically compare the pharmacological effects of fentanyl versus morphine in patients with STEMI undergoing primary PCI after pre-treatment with a potent oral $P2Y_{12}$ receptor inhibitor. The present study suggests potential differences in the pharmacological responses to ticagrelor between STEMI patients who received fentanyl or morphine for pain relief after ticagrelor pre-treatment. Overall, peak and time-to-peak plasma concentrations for ticagrelor and its major active metabolite AR-C124910XX after ticagrelor pre-treatment tended to be numerically higher and faster, respectively, among STEMI patients treated with fentanyl as compared to those receiving morphine. In addition, total exposures to ticagrelor and AR-C124910XX within 6 hours of ticagrelor pre-treatment were numerically greater among patients treated with fentanyl versus morphine. The observed numerical differences in ticagrelor pharmacokinetic profiles between fentanyl- and morphine-treated patients yielded a significantly increased platelet inhibition at 4 hours after ticagrelor pre-treatment among patients treated with fentanyl as compared to those receiving morphine. Interestingly, the analgesic effect of fentanyl-treated patients was similar to the effect observed with morphine, which lends further support to the preferential use of fentanyl rather than morphine in symptomatic STEMI patients undergoing primary PCI.

Limitations of the study

The results of the present study should be interpreted bearing in mind several limitations. Due to the premature termination of the trial and the smaller than anticipated sample size, the study results should be interpreted with appropriate caution and considered as hypothesis-generating. Notwithstanding, our pharmacodynamic findings suggest potential for an improved platelet inhibition at 4 hours with fentanyl after ticagrelor LD administration among STEMI patients as compared to morphine. The present study was not powered to assess pain outcomes between the fentanyl and morphine groups. As per study protocol, we defined HTPR as PRU $\geq$ 240 assessed by VerifyNow® platelet function assay according to consensus evidence available at the time of the study design [15]. However, we found similar results with regards to platelet reactivity when defining HTPR as PRU $\geq$ 208. Finally, this study was not powered for clinical endpoints, and larger studies are needed to explore whether the observed differences in ticagrelor pharmacodynamic and pharmacokinetic profiles induced by fentanyl versus morphine may translate into different clinical outcomes.

Conclusions

In patients with STEMI undergoing primary PCI after ticagrelor pre-treatment, fentanyl did not improve platelet inhibition at 2 hours compared with morphine. Taking into account the loss of power due to premature study termination, we found pharmacodynamic and pharmacokinetic evidence that fentanyl has the potential to reduce ticagrelor absorption delay and improve platelet inhibition compared to morphine. Future, properly powered studies should investigate the comparative clinical effects of fentanyl versus morphine in symptomatic STEMI patients undergoing primary PCI.

no role in the study data analysis or interpretation. The data supporting these findings are available from the corresponding author on reasonable request.

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