Despite the lack of rigorous studies designed to assess the effect of morphine administration in patients with acute myocardial infarction, clinical practice guidelines for the management of patients with ST-segment–elevation myocardial infarction (STEMI) strongly recommend morphine for analgesia.\textsuperscript{1,2} This recommendation derives only from expert opinion.

In patients with STEMI undergoing primary percutaneous coronary intervention (PPCI), a significant number of drugs are usually administered, thereby raising the potential risk for drug–drug interaction between morphine and antiplatelet agents. We sought to assess platelet inhibition after a loading dose of the currently recommended antiplatelet agents in ST-segment–elevation myocardial infarction patients according to morphine use.

**Background**—Morphine is recommended in patients with ST-segment–elevation myocardial infarction, including those undergoing primary percutaneous coronary intervention. Suboptimal antiplatelet effect during and after primary percutaneous coronary intervention is associated with increased thrombotic complications. It was hypothesized a potential drug–drug interaction between morphine and antiplatelet agents. We sought to assess platelet inhibition after a loading dose of the currently recommended antiplatelet agents in ST-segment–elevation myocardial infarction patients according to morphine use.

**Methods and Results**—Three hundred patients undergoing primary percutaneous coronary intervention receiving either prasugrel (n=95) or ticagrelor (n=205) loading dose had platelet reactivity assessed by VerifyNow 1, 2, and 4 hours after loading dose. Patients treated with morphine (n=95; 32%) had a higher incidence of vomit (15\% versus 2\%; \(P=0.001\)). P2Y\textsubscript{12} reactivity units 2 hours after the loading dose was 187 (153–221) and 133 (102–165) in patient with and without morphine (\(P<0.001\)); the difference persisted after excluding patients with vomit (\(P<0.0001\)). High residual platelet reactivity (P2Y\textsubscript{12} reactivity units \(\geq 208\)) at 2 hours was found in 53\% and 29\% patients with and without morphine (\(P<0.001\)) and without difference between prasugrel and ticagrelor patients. The independent predictors of high residual platelet reactivity at 2 hours were morphine use (odds ratio, 2.91 [1.71–4.97]; \(P<0.0001\)) and age (odds ratio, 1.03 [1.01–1.05]; \(P=0.010\)). Morphine remained associated with high residual platelet reactivity after propensity score adjustment (c-statistic, 0.68; 95\% confidence interval, 0.66–0.70; \(P=0.879\) for Hosmer–Lemeshow test).

**Conclusions**—In patients with ST-segment–elevation myocardial infarction, morphine use is associated with a delayed onset of action of the oral antiplatelet agents. This association persisted after adjusting for the propensity to receive morphine and after excluding patients with vomit.\textsuperscript{3} (Circ Cardiovasc Interv. 2015;8:e001593. DOI: 10.1161/CIRCINTERVENTIONS.114.001593.)

**Key Words:** infarction \(\bullet\) morphine \(\bullet\) platelets \(\bullet\) prasugrel \(\bullet\) stent \(\bullet\) ticagrelor

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WHAT IS KNOWN

- In acute ST-segment-elevation myocardial infarction, both antiplatelet agents and morphine are recommended therapies in the first few hours. A drug-to-drug interaction has been postulated but not established.

WHAT THE STUDY ADDS

- This study demonstrates a drug-to-drug interaction between morphine and the new P2Y12 platelet inhibitors: prasugrel and ticagrelor. Morphine use is associated with delayed onset of action of these oral antiplatelet agents.
- The association between morphine and delayed onset of action of orally administered antiplatelet agents persisted after adjusting for the propensity to receive morphine and after excluding patients with vomiting.

Methods

Study Design

This study was a patient-level integrated analysis exploring the effect of morphine on platelet reactivity in STEMI patients undergoing PPCI treated with ticagrelor or prasugrel from 5 studies in which residual platelet reactivity was assessed by VerifyNow after LD. This study included published trials by Parodi et al3,5 and Alexopoulos et al6,7 and an unpublished study from Catania University. The studies were approved by the local ethical committees. All patients gave informed consent. We asked the study principal investigators to stratify each enrolled patient according to morphine use before antiplatelet agent LD and to look for occurrence of vomiting (defined as forceful expulsion of gastric content by the mouth within 2 hours from prasugrel or ticagrelor LD).

Patient Population

A diagnosis of STEMI within 12 hours of symptoms onset was required for study entry. Exclusion criteria were (1) age <18 year, (2) active bleeding or bleeding diathesis, (3) any previous transient ischemic attack or stroke, (4) administration of ticlopidine, clopidogrel, prasugrel, ticagrelor, or glycoprotein IIb/IIIa inhibitors in the week before the index event, (5) need for chronic anticoagulant therapy, (6) known relevant hematologic deviations, (7) life expectancy <1 year, (8) known severe liver or renal disease, and (9) hemodynamic instability. The study flow chart is reported in Figure 1. At 3 participating institutions, out of 496 STEMI patients, we analyzed 300 subjects who were P2Y12 inhibitor naïve and received prasugrel 60 mg (n=95) or ticagrelor 180 or 360 mg LD (n=205) before PPCI. Patients who received an increased ticagrelor LD were included in 2 randomized studies approved by the local Ethic Committees.3,6 The LD was given as soon as possible in the emergency room or in the Cath-Laboratory. Dual antiplatelet therapy (aspirin 100 mg OD in combination with prasugrel 5–10 mg OD or ticagrelor 90 mg BID) was recommended for 12 months.

Concomitant Antithrombotic Medications

The following antithrombotic agents were given on top of prasugrel or ticagrelor at the time of PPCI: (a) aspirin 300 to 500 mg LD followed by 100 mg OD; (b) bivalirudin 0.75 mg/kg bolus followed by 1.75 mg/kg/h infusion during PPCI or unfractionated heparin 70 U/kg bolus followed by additional boluses to achieve an activated clotting time of 250 to 300 seconds during PPCI; (c) the use of glycoprotein IIb/IIIa inhibitors was not allowed.

Platelet Function Tests

Residual platelet reactivity was assessed 1, 2, and 4 hours after LD by means of the VerifyNow assay. High residual platelet reactivity (HRPR) was defined as a P2Y12 reactivity units (PRU) ≥208.5 We also evaluated the number of patients with suboptimal platelet inhibition according to the previously adopted cut-off of 230.

End Points

The primary study end-point was residual platelet reactivity by PRU VerifyNow 2 hours after LD. Secondary end-points were (1) the percentage of patients with HRPR at 2 hours from administration of the LD and (2) incidence of vomiting.

Statistical Analysis

Categorical data are presented as frequencies and group percentages. Continuous data with normal and skewed distribution are presented as means±SD and medians (first to third quartile), respectively. The Kolmogorov–Smirnov test was used to examine data distribution normality. For the purpose of the current analysis, patients’ characteristics are presented by morphine use.

The multivariable analysis used to evaluate the independent contribution of clinical characteristics to HRPR at 2 hours was performed by forward stepwise binary logistic regression. A significance level of 0.05 was required for a variable to be included in the multivariate model, whereas 0.20 was the cut-off value for exclusion. Moreover, variables known to affect platelet reactivity were forced into the final model. Candidate variables entered into the model were age (years), body mass index, diabetes mellitus, systolic blood pressure, bivalirudin administration, ticagrelor use, and morphine use. Odds ratios and 95% confidence intervals (CI) were calculated. A propensity score analysis was also performed with a logistic regression model from which the probability for morphine use was calculated for each patient to compensate for the nonrandomized administration of morphine. Variables that were significantly different between the 2 groups and those that are known to affect platelet reactivity were incorporated in the model: age (years), sex, body mass index, diabetes mellitus, smoking, killip class, systolic blood pressure, heart rate, anterior infarct location, and bivalirudin.9,10 Model discrimination was assessed with the c-statistic and goodness of fit with the Hosmer–Lemeshow test. Thereafter, a logistic regression analysis was performed to adjust HRPR for the propensity score used as a continuous covariate. PRU differences between groups were analyzed via a mixed linear model with time and morphine use as fixed effects, propensity score as covariate, patient and study as random effects to account for within-study correlation. To account for within-study correlation of participants, we also modeled the study as a random intercept.11 Adjusted estimates for HRPR (presented as risk ratios with corresponding P values) were derived from a generalized estimating equations model using log-Poisson function with robust variance estimator, with time as within-subject effect, morphine treatment as fixed effect, and propensity score as a covariate, using an autoregressive correlation matrix. All tests were 2-tailed, and statistical significance was considered for P values <0.05. All statistical analyses were performed using SPSS for Windows (version 16.0, SPSS Inc, Chicago, IL) and NCSS 8 (NCSS, Kaysville, Utah).

Results

Baseline and Procedural Characteristics

Overall, we analyzed 95 and 205 STEMI patients treated with or without morphine, respectively, according to the decision of the attending physicians in the ambulance or in the
emergency room. Median total morphine dose per patient was 4 (2–6) mg with a range of 2 to 12 mg. Demographic and clinical characteristics of patients by morphine use are presented in Table 1. Prasugrel or ticagrelor LD was given in 24% patients in the emergency room and in 76% patients in the Cath Laboratory, without differences between the 2 groups. During PPCI, bivalirudin was used in 204 (68%) patients; the remaining subjects received unfractionated heparin. There were no significant difference in the baseline characteristics between patients with and without morphine, but a lower body mass index, a more prevalent bivalirudin use, and a trend toward a higher systolic blood pressure in morphine-treated patients (Table 1). As expected, patients treated with morphine had a higher incidence of vomit (15% versus 2%; \( P=0.001 \)) as compared with those without.

### Residual Platelet Reactivity

Patients who received morphine had higher PRU during study measurements as compared with those who did not: 182.3 PRU (95% CI, 164.2–200.3) versus 140.3 PRU (95% CI, 128.2–152.4), with a mean difference of 42.0 PRU (95% CI, 19.8–64.1), \( P<0.001 \) (Figure 2). The PRU values at 2 hours (primary end-point) were 187.3 (153.4–221.2) and 133.7 (102.3–165.0) in patients with and without morphine (\( P<0.001 \)); the difference between the 2 study groups persisted after excluding patients with vomit (222.0 [89.0–282.0] versus 107.0 [29.5–225.5]; \( P<0.0001 \)). The PRU difference was still present at 4 hours (\( P=0.04 \)). In ticagrelor-treated patients (excluding patients who received prasugrel), PRU 2 hours after LD was 231 (114–287) and 110 (33–226) in patients with and without morphine (\( P<0.001 \)). Overall, HRPR at 2 hours was found in 53% and 29% patients with and without morphine (\( P<0.001 \); Table 2), without differences between prasugrel and ticagrelor patients (39% versus 37%; \( P=0.72 \)). Generalized estimating equations modeling revealed that morphine use was overall associated with an increased risk of HRPR using either the 208 or the 230 threshold: risk ratio=1.55 (95% CI, 1.28–1.87), \( P<0.001 \) and risk ratio=1.44 (95% CI: 1.20–1.86), \( P<0.001 \) respectively.

The independent predictors of HRPR at 2 hours were morphine use (odds ratio, 2.91 [1.71–4.97]; \( P<0.0001 \)) and age (odds ratio, 1.03 [1.01–1.05]; \( P=0.010 \)). Morphine remained significantly associated with HRPR (odds ratio, 1.89 [1.40–2.56]; \( P<0.001 \)) after propensity score adjustment (c-statistic, 0.68; 95% CI, 0.66–0.70; \( P=0.879 \) for Hosmer–Lemeshow test).

### In-Hospital Outcome

Clinical events observed during the hospital stay are reported in Table 3. Possibly reflecting the small sample size and the limited time of observation, there was no significant difference in event rates between the 2 study groups.

### Discussion

The study results can be summarized as follow:

1. In patients with STEMI, morphine use is associated with a delayed onset of action of the oral antiplatelet agents.
2. The drug-to-drug interaction persisted after adjusting for the probability to receive morphine and after excluding patients with vomit.
3. The effect of morphine on platelet inhibition was consistent in prasugrel and ticagrelor patients.

In the present multicenter pharmacodynamic study, morphine use was associated with a delayed onset activity of the new oral antiplatelet agents, prasugrel and ticagrelor. In fact, morphine-treated patients showed higher residual platelet reactivity values 1, 2, and 4 hours after drug LD. Of note, morphine has a half live of \( \approx 2 \) hours, and 3 half-lives are needed to decrease by \( \approx 90\% \) the plasma concentration. Thus, \( >6 \) hours are needed to spontaneously reverse morphine effect. Naloxone (morphine synthetic reversal agent) was not used in our study patients. The negative effect of morphine on platelet inhibition is not only confined when vomit occurs as a side effect of its use because after excluding patients with vomit, morphine-treated subjects still clearly have higher residual platelet reactivity as compared with subjects who did not receive morphine. The effect was consistent with the P2Y\textsubscript{12} receptor irreversible inhibitor prasugrel and the nonthienopyridine reversible
antiplatelet agent ticagrelor. Given the well-known delayed onset of action and effect variability of clopidogrel as compared with prasugrel and ticagrelor, it is easy to anticipate a similar and even more clinically evident interaction between morphine and clopidogrel. However, the use of the more effective new oral antiplatelet agents is strongly recommended and increasing in the setting of STEMI. The morphine–antiplatelet agent interaction is likely a non-drug-specific phenomena and related to the inhibition of the normal muscular activity of the stomach and the intestines, which may lead to vomit or delayed gastric emptying, which in turn delays absorption and decreases peak plasma levels of orally administered drugs.

Along with morphine, age was confirmed to be a strong predictor of HRPR. On the other hand, the type of antiplatelet agent did not result as an independent predictor of HRPR. Thus, ticagrelor, even if it is adsorbed as an active compound without the need for a metabolic activation at the liver level,
Table 2. High Residual Platelet Reactivity Rates at Study Time Points

<table>
<thead>
<tr>
<th>Time Points</th>
<th>No Morphine Use (n=205)</th>
<th>Morphine Use (n=95)</th>
<th>Adjusted RR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hour 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥208 PRU</td>
<td>92 (59.7)</td>
<td>53 (79.1)</td>
<td>1.32 (1.10–1.59)</td>
<td>0.003</td>
</tr>
<tr>
<td>≥230 PRU</td>
<td>84 (54.5)</td>
<td>44 (65.7)</td>
<td>1.17 (0.93–1.49)</td>
<td>0.23</td>
</tr>
<tr>
<td>Hour 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥208 PRU</td>
<td>59 (29.2)</td>
<td>47 (52.8)</td>
<td>1.89 (1.40–2.56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥230 PRU</td>
<td>49 (24.3)</td>
<td>42 (47.2)</td>
<td>2.06 (1.46–2.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hour 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥208 PRU</td>
<td>12 (9.5)</td>
<td>17 (24.3)</td>
<td>2.11 (1.06–4.21)</td>
<td>0.03</td>
</tr>
<tr>
<td>≥230 PRU</td>
<td>7 (5.6)</td>
<td>13 (18.6)</td>
<td>2.77 (1.14–6.73)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Data are expressed as n (%). CI indicates confidence interval; PRU, P2Y12 reaction units; and RR, risk ratio.

Figure 2. Platelet reactivity over time of patients who received morphine or non-morphine. PRU was significantly higher in the morphine group than in the non-morphine group (P<0.001). There was also a significant effect in platelet reactivity over time (P<0.001). No significant morphine-by-time interaction was observed. Means and 95% confidence intervals are displayed. PRU indicates P2Y12 reaction units.

showed a similar delayed of action, suggesting a similar delayed adsorption as compared with prasugrel. This fact is also reinforced by the fact that some patients enrolled in this study received an increased ticagrelor LD. As a matter of fact, in the administration of ticagrelor in the cath laboratory or in the ambulance for new ST-elevation myocardial infarction to open the coronary artery (ATLANTIC) Trial, patients who did not receive morphine had a significant improvement in time to open the coronary artery (ATLANTIC) Trial, patients who did not receive morphine had a significant improvement in the ECG-based primary end point, with a significant P value for interaction between morphine use and time of ticagrelor administration.16

We may also hypothesize that patients who received morphine might be subjects at higher risk. However, after adjusting for the baseline clinical characteristics, morphine use remained associated with HRPR 2 hours after drug LD. This association was confirmed after the calculation of the probability for each patient to receive morphine and using the obtained propensity score in the multivariable model. However, it is not possible to rule out that in sicker patients, hemodynamic disarrangement, adrenergic activation, systemic vasoconstriction with the reduction of blood volume to the abdomen may contribute to the delayed drug adsorption and to the reduced platelet inhibition.

Table 3. In-Hospital Outcomes of Patients Treated With or Without Morphine

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No Morphine Use (n=205)</th>
<th>Morphine Use (n=95)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>7 (3%)</td>
<td>2 (2%)</td>
<td>0.53</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>0.58</td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (1%)</td>
<td>0 (0%)</td>
<td>0.33</td>
</tr>
<tr>
<td>TIMI major bleeding</td>
<td>4 (2%)</td>
<td>1 (1%)</td>
<td>0.57</td>
</tr>
<tr>
<td>TIMI minor bleeding</td>
<td>7 (3%)</td>
<td>7 (6%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>8 (8%)</td>
<td>1 (1%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Contrast induced nephropathy</td>
<td>7 (7%)</td>
<td>3 (5%)</td>
<td>0.66</td>
</tr>
</tbody>
</table>

TIMI indicates thrombolysis in myocardial infarction.

Recent data suggest that suboptimal platelet inhibition early after PPCI may be associated with thrombotic complications, including stent thrombosis.17 Given the key importance of platelet inhibition in patients treated by PPCI for STEMI and the absence of data that may support a potential clinical benefit of morphine in patients with acute myocardial infarction, more caution should be used regarding morphine administration in STEMI patients and a restricted morphine use seems to be reasonably recommended. Other strategies beside morphine may reduce chest pain levels in STEMI patients. It has been documented since a long time that β-blockers,18 and nitrates19 are able to reduce acute myocardial infarction–related chest pain. Aspirin itself has relevant analgesic properties, and alternative analgesics might be considered in STEMI patients. Finally, myocardial ischemia relief (ie, reperfusion) is the definitive chest pain control strategy.

Our study must be evaluated in light of some limitations. First, this was not a randomized comparison, and a further randomized study is needed to confirm the potential effect of morphine use in STEMI patients undergoing PPCI. Second, this is a pharmacodynamic study and the small sample size does not allow to assess the potential effect of morphine on clinical end-points. HRPR is not precisely equivalent to reduced antiplatelet effect: pretreatment aggregability may also be important. Moreover, to confirm impaired drug absorption, a pharmacokinetic analysis should have been performed. However, a small recent study, obtained in 24 healthy volunteers, documented that morphine delays clopidogrel absorption and decreases plasma levels of clopidogrel active metabolite.20 Finally, unmeasured residual bias and the risk of overfitting cannot be excluded even in our parsimonious multivariable model. These limitations notwithstanding the present study provides several unique and potentially important insights in the treatment of STEMI patients by PPCI and newer antiplatelet agents.

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Disclosures

Dr Parodi reported receiving consulting or lecture fees from Daiichi Sankyo/Eli Lilly, AstraZeneca, Bayer, and The Medicine Company. Dr Capranzano reports receiving consulting or lecture fees from Daiichi Sankyo/Eli Lilly, AstraZeneca, and The Medicine Company and serving on the advisory board of Daiichi Sankyo/Eli Lilly. Dr Capranzano reports receiving consulting or lecture fees from Daiichi Sankyo/Eli Lilly, Bayer, Boehringer Ingelheim, and The Medicine Company and serving on the advisory board of Daiichi Sankyo/Eli Lilly. Dr Antoniucci reported receiving consulting fees from Daiichi Sankyo/Eli Lilly and The Medicines Company. Dr Alexopoulos reported receiving lecture fees from AstraZeneca. The other authors report no conflict.

References


Morphine Is Associated With a Delayed Activity of Oral Antiplatelet Agents in Patients With ST-Elevation Acute Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

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