

DRUG INTERACTIONS

Abciximab as a bridging strategy to overcome morphine–prasugrel interaction in STEMI patients

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OBJECTIVE

The present study investigated whether the glycoprotein (GP)IIb/IIIa receptor blocker abciximab might be a successful bridging strategy to achieve adequate levels of platelet inhibition rapidly in cases where prasugrel is used in morphine-pretreated ST-elevation myocardial infarction (STEMI) patients.

METHODS

In a prospective observational cohort study, 32 patients presenting with STEMI were given prasugrel at a loading dose of 60 mg. Patients were stratified into four groups, according to morphine and/or abciximab use. Adenosine diphosphate (ADP)-induced platelet aggregation was measured at four time points: at baseline, and at 2 h, 1 day and 2 days after prasugrel loading.

RESULTS

Morphine use was associated with a three-fold higher level of ADP-induced platelet aggregation 2 h after prasugrel loading compared with no morphine/no abciximab ($P = 0.019$). However, when abciximab was infused in the catheterization laboratory, the effect of morphine on ADP-induced platelet aggregation disappeared ($P = 0.884$). This interaction was also seen in the presence of high on-treatment platelet reactivity (HTPR) at 2 h; while HTPR was seen in 88% of morphine users/no abciximab users, it was found in only 17–20% in the three other groups ($P = 0.003$). The effect of morphine disappeared by day 1–2.

CONCLUSION

The infusion of the GPIIb/IIIa receptor blocker abciximab allows immediate and efficient platelet inhibition in STEMI patients concomitantly receiving the oral ADP receptor blocker prasugrel and morphine.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- A drug–drug interaction between morphine and the three P2Y₁₂ receptor inhibitors clopidogrel, prasugrel and ticagrelor has been reported.
- GPIIb/IIIa receptor blockers are rapidly acting drugs, with a potent inhibitory effect on the final common pathway of platelet aggregation, and also on signalling events downstream of ADP-induced platelet aggregation.

WHAT THIS STUDY ADDS

- A single dose of intravenous morphine was associated with a delay in the onset of prasugrel action.
- The morphine–prasugrel interaction was apparent at an early stage (at 2 h) after prasugrel administration, and did not persist for longer than 1 day after a single morphine administration.
- Abciximab reduced platelet aggregation during a primary percutaneous coronary intervention when morphine was administered concomitantly with prasugrel, and might be a useful bridging strategy to improve platelet inhibition in such patients.

Introduction

The concomitant administration of multiple drugs is common in patients presenting with ST-elevation myocardial infarction (STEMI), which could lead to drug–drug interactions. Some of these interactions may occur for P2Y₁₂ receptor inhibitors, with the possible consequence of insufficient inhibition of platelet function in a setting where maximum inhibition would be desirable [1, 2].

Morphine, recommended for pain relief, is frequently used in STEMI patients. Recently, an interaction between morphine and the P2Y₁₂ receptor inhibitors clopidogrel, prasugrel and ticagrelor has been reported [3–6]. This is probably due to the morphine-induced inhibition of gastric emptying, which might delay the absorption of other oral drugs, prolonging the time to reach peak concentration (T_{max}) and therefore slowing their onset of action [7].

Intravenous glycoprotein (GP) IIb/IIIa receptor blockers are also commonly used in patients with STEMI. GPIIb/IIIa receptor blockers are rapidly acting drugs, with a potent inhibitory effect on the final common pathway of platelet aggregation, and also on signalling events downstream of ADP-induced platelet aggregation [8]. Therefore, the administration of intravenous GPIIb/IIIa receptor blockers may overcome a delayed onset of action of orally administered drugs, including P2Y₁₂ receptor blockers, in the setting of morphine coadministration. Against this background, we aimed to investigate whether the concomitant use of prasugrel and abciximab might be a successful bridging strategy to achieve sufficient inhibition of platelet aggregation rapidly in cases where prasugrel is used in morphine-pretreated STEMI patients undergoing primary percutaneous coronary intervention (PCI).

Methods

Study design

This prospective observational cohort study was performed at the Medical University of Vienna. The ethics committee of the Medical University of Vienna approved the study protocol in accordance with the Declaration of Helsinki. Participants were recruited into the study between May 2013 and

June 2015. Inclusion criteria comprised the provision of written informed consent before study entry, treatment with an in-hospital loading dose of prasugrel for an acute STEMI, receipt of primary PCI and being aged >18 years. The exclusion criterion was participation in interventional trials. Thirty-two consecutive patients fulfilling the inclusion and exclusion criteria were enrolled. All patients received a loading dose of prasugrel (60 mg) in the emergency department or in the catheter laboratory followed by a once-daily dose of 10 mg prasugrel. Intravenous morphine was administered in the ambulance before reaching the hospital or in the emergency department, and its use was at the discretion of the treating physician. An abciximab bolus was administered in the catheterization laboratory according to the current recommendations, at the discretion of an interventional cardiologist, and maintained for 12 h as a continuous infusion according to the label. Intravenous aspirin (250 mg) was administered to all patients during the prehospital phase. Blood samples were obtained from patients at baseline (before the loading dose of prasugrel), and then after 2 h, 1 day and 2 days at 8 a.m. (Figure 1A).

Impedance aggregometry

Whole-blood aggregation was determined using multiple electrode aggregometry on a new-generation impedance aggregometer (Multiplate Analyzer, Roche, Munich, Germany). The system detects the change in electrical impedance due to the adhesion and aggregation of platelets on two independent electrode-set surfaces in the test cuvette, as described [9–11]. We used hirudin as anticoagulant, and adenosine diphosphate (ADP) and arachidonic acid (AA) as agonists. A 1:2 dilution of whole blood anticoagulated with hirudin and 0.9% NaCl was stirred at 37 °C for 3 min in the test cuvettes; ADP (6.4 μM) or AA (0.5 mM) was then added and the increase in electrical impedance was recorded continuously for 6 min [12, 13]. The mean values of the two independent determinations were expressed as U (units). According to the position documents, values >46 U were assigned as high on-treatment platelet reactivity (HTPR) [1, 14, 15].

Study endpoints

The primary endpoint was ADP-induced platelet aggregation. For descriptive purposes, the incidence of myocardial

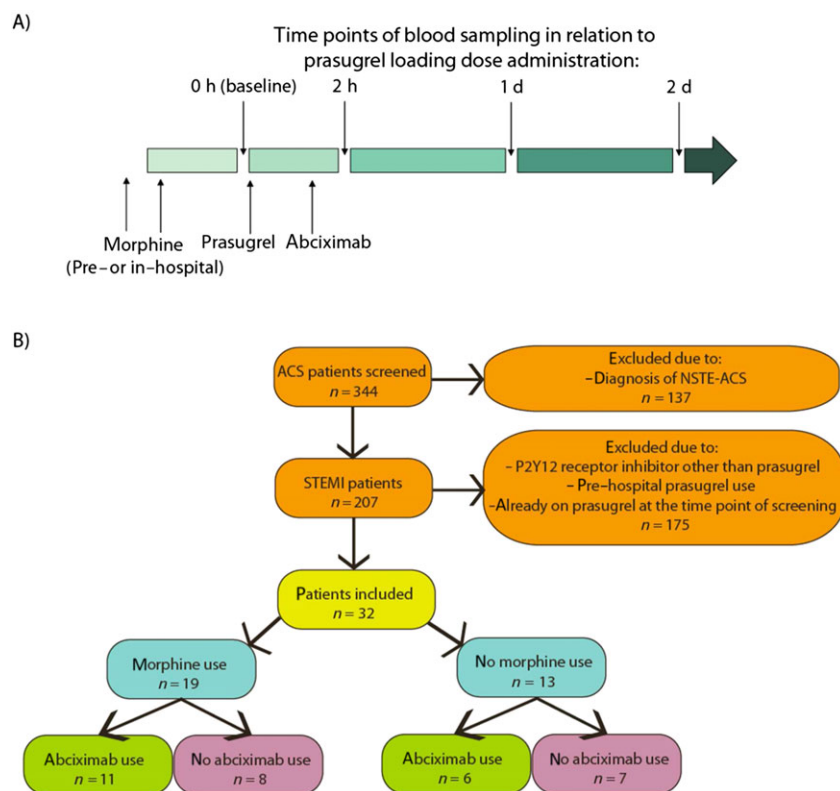


Figure 1

Study design. (A) Time points of drug administration and blood sampling. (B) Flow of participants in the study. ACS, acute coronary syndrome; d, day; NSTEMI-ACS, non ST-elevation ACS

infarction and major cardiac adverse events (MACE: myocardial infarction, cardiac death and stroke) was recorded and reported during the hospital stay. Myocardial infarction was defined according to the universal definition [16].

Statistical analysis

Based on threefold higher ADP aggregation values in morphine users compared with non-users, 2 h after clopidogrel loading [standard deviation (SD) = 10] [3], we estimated that, with 28 patients (seven patients per group), our study had 80% power to detect significant differences (two-sided P value < 0.05). Normal distribution was tested using the Kolmogorov–Smirnov test. Data were expressed as mean, SD, 95% confidence intervals (CIs), median or interquartile range (IQR), as appropriate. Statistical comparisons were performed using the Mann–Whitney U test, paired Wilcoxon test and χ^2 test when applicable. All statistical calculations were performed using the commercially available SPSS Version 21.0 statistical software (IBM, Armonk, NY, USA).

Results

Patient demographics

Patient flow through the study is shown in Figure 1B. Of 344 acute coronary syndrome patients screened, 32 fulfilled the inclusion criteria and were included in the study. The majority

of individuals had the typical risk factors associated with STEMI: hypertension (62%), hyperlipidaemia (35%), smoking (86%) and diabetes mellitus (14%) (Table 1). Among included patients, 19 (59%) were treated with intravenous morphine (at doses: 10 mg in 17 patients, 5 mg in one and 15 mg in one) before prasugrel loading. There were no differences in demographic data between patients treated with and without morphine. Abciximab was used in 17 patients (57%) in the catheterization laboratory and its administration was distributed equally between patients treated with and without morphine. All patients underwent a successful primary PCI.

ADP-induced platelet aggregation

In the overall population, the median level of ADP-induced platelet aggregation decreased by 66% 2 h after prasugrel loading compared with baseline (27 U, IQR: 15–57 U vs. 80 U, IQR: 73–96, respectively; $P < 0.001$; Figure 2). Platelet aggregation achieved the lowest level on day 1 after loading (7 U, IQR: 3–12 U; 91% decrease compared with baseline; $P < 0.001$; 74% decrease compared with value at 2 h; $P = 0.001$), and stayed in the same range on day 2 after loading (15 U; IQR: 5–21; $P = 0.235$ compared with day 1; Figure 2).

ADP-induced platelet aggregation in relation to abciximab and morphine use

Patients were stratified into morphine users vs. non-users, and patients with or without abciximab infusion. The use of

Table 1

Patient demographics

Patient demographics	Overall <i>n</i> = 32	With morphine <i>n</i> = 19	Without morphine <i>n</i> = 13	<i>P</i>
Age (years)	60 ± 11	58 ± 11	63 ± 10	0.17
Gender (male) <i>n</i> (%)	29 (93)	18 (94)	11 (84)	0.69
Risk factors/past medical history <i>n</i> (%)				
Hypertension	18 (62)	10 (56)	8 (72)	0.36
Hyperlipidaemia	10 (35)	7 (39)	3 (27)	0.52
Smoking	25 (86)	15 (83)	10 (91)	0.57
Family history of CAD	10 (34)	9 (50)	5 (38)	0.25
Diabetes mellitus	4 (14)	3 (17)	1 (9)	0.57
Prior PCI	4 (13)	3 (18)	1 (9)	0.53
Prior myocardial infarction	6 (21)	4 (22)	2 (18)	0.80
Peripheral arterial occlusive disease	3 (10)	1 (6)	2 (18)	0.28
Cerebrovascular disease	1 (3)	1 (5)	0 (0)	0.43
Laboratory data (mean ± SD)				
Platelet counts ($\times 10^9 \text{ l}^{-1}$)	224 ± 67	222 ± 73	229 ± 61	0.90
C reactive protein (mg dl⁻¹)	0.83 ± 1.12	0.63 ± 1.14	1.16 ± 1.06	0.07
White blood cell count ($\times 10^9 \text{ l}^{-1}$)	12.26 ± 3.56	12.27 ± 3.89	12.24 ± 3.07	0.80
Creatinine (mg dl⁻¹)	0.98 ± 0.27	1.02 ± 0.32	0.93 ± 0.18	0.64
Haemoglobin (g dl⁻¹)	14.9 ± 1.03	14.9 ± 0.86	14.9 ± 1.33	0.55
Fibrinogen (mg dl⁻¹)	384 ± 85	382 ± 76	386 ± 101	0.78
Concomitant medications at 2 h <i>n</i> (%)				
Aspirin	32 (100)	19 (100)	13 (100)	
Proton pump inhibitors	23 (80)	15 (83)	8 (73)	0.49
β-blockers	23 (80)	15 (83)	8 (72)	0.59
Statins	25 (86)	16 (90)	9 (82)	0.49
Angiotensin-converting enzyme inhibitors	23 (80)	14 (78)	9 (82)	0.79
Calcium channel blockers	3 (10)	1 (6)	2 (18)	0.28
Angiographic data				
GPIIb/IIIa blocker (abciximab) during the PCI	17 (57)	11 (60)	6 (55)	0.78
Heparin	32 (100)	19 (100)	13 (100)	
Bivalirudin	0 (0)	0 (0)	0 (0)	
Primary PCI	32 (100)	19 (100)	13 (100)	
Number of stents per patient	1.57 ± 1.19	1.79 ± 1.31	1.18 ± 0.87	0.23
Total stent length (mm)	35.9636.0 ± 34.051	38.4 ± 40.0	30.8 ± 16.384	0.78

Data are reported as mean ± standard deviation (SD), *n* (number of patients) or percentages. CAD, coronary artery disease; GP, glycoprotein; PCI, percutaneous coronary intervention.

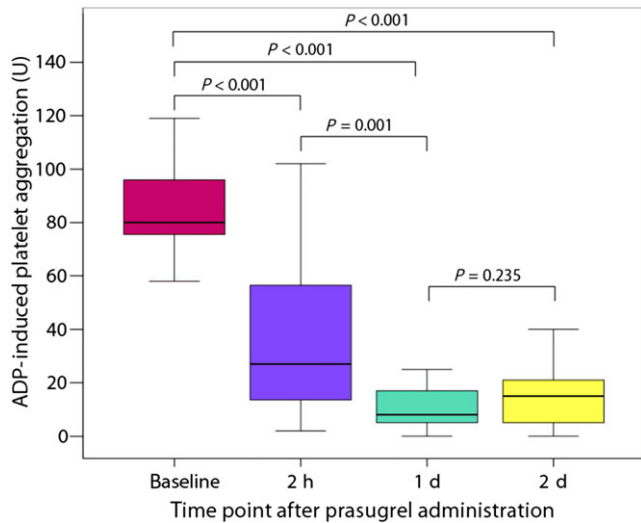


Figure 2

Adenosine diphosphate (ADP)-induced platelet aggregation assessed by multiple electrode aggregometry in relation to the time of prasugrel loading. d, day

morphine was associated with threefold higher median levels of ADP-induced aggregation at 2 h compared with no morphine use among the non-abciximab group (68 U; IQR: 50–94 vs. 23 U; IQR: 16–46; $P = 0.019$; Figure 3). By contrast, the infusion of abciximab appeared to counteract the negative effect of morphine (16 U; IQR: 8–34 vs. 16 U; IQR: 7–41; $P = 0.884$; Figure 3). This interaction was also prominent when HTPR rates at 2 h were taken into account: while patients who received morphine but not abciximab had an

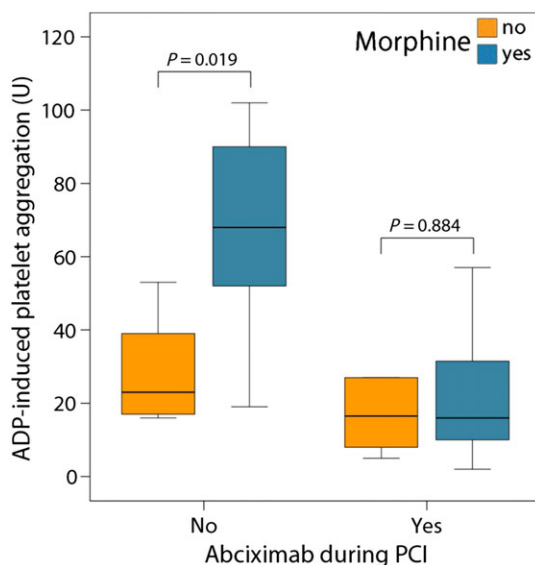


Figure 3

Adenosine diphosphate (ADP)-induced platelet aggregation values stratified by morphine and abciximab administration, measured 2 h after prasugrel loading

HTPR rate of 88%, the HTPR rate was only 17–20% in the three other groups ($P = 0.003$; Figure 4). The negative effect of morphine disappeared by day 1–2, independent of abciximab use (Figure 5).

AA-induced platelet aggregation

As expected, morphine did not have an effect on AA-induced platelet aggregation (data not shown), probably because aspirin given intravenously produces a rapid effect onset in patients with myocardial infarction [17].

In-hospital outcome

During the hospital stay, no ischaemic events and no major bleeding events occurred. Minimal bleeding events (epistaxis and skin haematoma; $n = 9$) were reported predominantly in patients who received abciximab ($n = 7$ vs. $n = 2$ for abciximab- vs. no-abciximab-treated patients; $P = 0.072$).

Discussion

The central findings of the present study investigating the interaction between morphine, abciximab and prasugrel were:

- 1 A single dose of intravenous morphine was associated with a delayed onset of prasugrel action.
- 2 The morphine–prasugrel interaction was apparent early on (at 2 h) after prasugrel administration, and did not persist longer than 1 day after a single morphine administration.
- 3 Abciximab successfully reduced platelet aggregation for primary PCI when morphine was administered concomitantly with prasugrel, and might be a useful bridging strategy to improve platelet inhibition in such patients.

Decreased gastrointestinal absorption is the major limitation to the onset of action of orally administered antiplatelet agents in STEMI patients, and apparently cannot be overcome by increasing the loading doses of P2Y₁₂ receptor inhibitors, as shown for ticagrelor [18, 19]. The morphine–P2Y₁₂

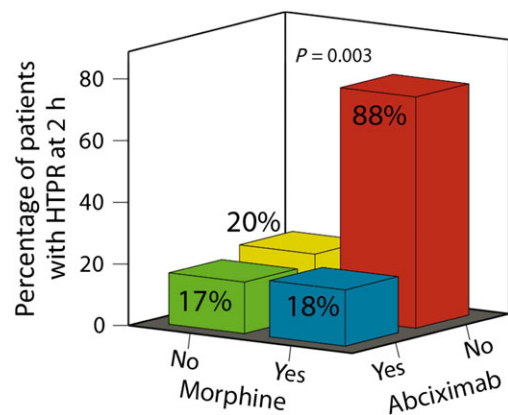


Figure 4

The proportion of patients with high on-treatment platelet reactivity (HTPR) stratified by morphine and abciximab administration, measured 2 h after prasugrel loading

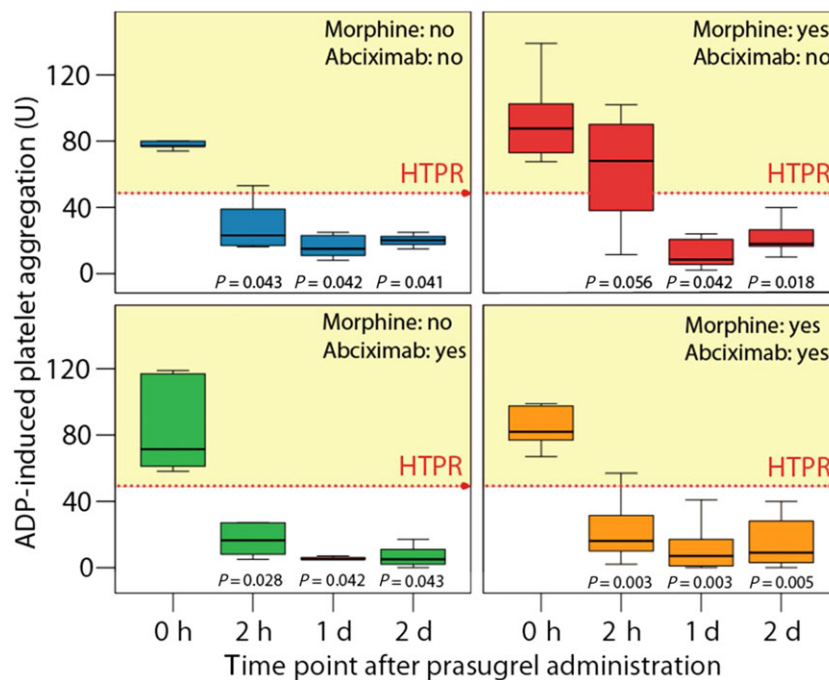


Figure 5

Adenosine diphosphate (ADP)-induced platelet aggregation stratified by morphine and abciximab administration, measured at various time points after prasugrel loading. HTPR, high on-treatment platelet reactivity. The *P* values given are for the comparison between baseline and other time points

receptor inhibitor interaction has been proposed as an explanation for this phenomenon [3–5, 20, 21]. The recently published randomized trial Influence of Morphine on Pharmacokinetics and Pharmacodynamics of Ticagrelor in Patients with Acute Myocardial Infarction (IMPRESSION) confirmed the negative impact of morphine on the pharmacokinetics and antiplatelet action of ticagrelor in patients presenting with an acute myocardial infarction [20]. By contrast, 5 mg of morphine primarily reduced and delayed the early bioavailability of ticagrelor in healthy volunteers but had no measurable impact on ticagrelor effects [21]. Concomitantly, morphine reduced the maximal concentration of the prasugrel active metabolite by only 31% but did not delay the onset of action of prasugrel in healthy subjects [6]. By contrast, morphine was associated with a reduction in the effects of prasugrel in patients with myocardial infarction, which has also been found in previous studies [4, 5]. Therefore, it seems reasonable that the negative impact of morphine on the antiplatelet effect of ADP receptor blockers is more pronounced in patients with acute myocardial infarction who have compromised gastrointestinal perfusion due to cardiac ischaemia than in healthy volunteers.

The highest rate of HTPR was observed at 2 h after prasugrel loading, which indicates the external validity of our findings [4, 5]. Morphine was significantly associated with HTPR, even after adjustment for other variables [5, 20]. In line with these findings, the morphine–prasugrel interaction was apparent 2 h after prasugrel administration in the present study, but not beyond day 1, which is also consistent with previous findings [3].

The clinically most important issue is whether the morphine–P2Y₁₂ receptor blocker interaction influences clinical outcomes. The Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) trial showed that prehospital administration of ticagrelor significantly improved the primary endpoint of ST-segment resolution only in patients not receiving morphine [22]. Despite this interesting finding of a primary negative trial, more studies are needed to confirm the possible negative impact of morphine administration on clinical outcome data in acute myocardial infarction.

The biological effect of morphine on orally administered antiplatelet drugs is likely to be due to the inhibition of gastric emptying [7]. In the present study, we demonstrated that the intravenous GPIIb/IIIa receptor inhibitor abciximab can be used as a potential bridging strategy in STEMI patients when rapid and efficient platelet inhibition is required. Our study in prasugrel-treated STEMI patients indicated that abciximab sufficiently inhibits platelet aggregation after morphine administration. By contrast, morphine use was associated with an 88% rate of HTPR 2 h after prasugrel intake, when abciximab was not infused. A large body of evidence suggests that HTPR is most common when clopidogrel is used but is also present following treatment with prasugrel and ticagrelor and is associated with thrombotic risk at follow-up [23–29]. HTPR is also predictive of intra- and periprocedural thrombotic events, even under prasugrel therapy in the acute setting with a large thrombus burden [30]. Therefore, the rationale for the immediate blocking of

platelet aggregation by abciximab infusion as a bridging strategy to overcome the delay of P2Y₁₂ receptor inhibitor action is based on the hypothesis that abciximab inhibits platelet activation downstream by preventing activation of platelet GPIIb/IIIa receptors. This concept has been successfully demonstrated in patients treated with clopidogrel and prasugrel in a pharmacodynamic study [8]. In smaller studies, platelet inhibition with GPIIb/IIIa receptor antagonists in individuals with HTPR reduced the incidence of major adverse cardiac events without increasing bleeding [31, 32]. Nevertheless, it remains to be shown whether the infusion of a GPIIb/IIIa receptor blocker for immediate platelet inhibition in addition to oral loading with an ADP receptor antagonist may improve the net clinical outcomes, when morphine is used. As bleeding is an independent determinant of short- and long-term mortality [33, 34], use of GPIIb/IIIa receptor blockers may be harmful. In the present study, which was not powered for clinical outcomes, abciximab was associated with more minimal bleeding events. Interestingly, a previous study indicated that patients at high risk of bleeding also had a net benefit from a GPIIb/IIIa receptor blocker [34]. It should therefore be explored whether the short-acting intravenous P2Y₁₂ receptor blocker cangrelor can also be a useful alternative in this setting [35], especially when GPIIb/IIIa receptor blockers are not indicated.

Limitation

The main limitation of the present study was its nonrandomized design. However, despite this limitation, the groups appeared to be reasonably well balanced. In addition, as it would not have been feasible in the setting of acute myocardial infarction, the study did not present the time course of the effect of morphine coadministration on the antiplatelet effect of prasugrel between 2 h postdosing and day 1 after admission. A further limitation of the present study was the fact that we used only one test for the assessment of antiplatelet efficacy – ADP-induced platelet aggregation.

Conclusion

Morphine use is associated with a delay in the onset of prasugrel action in STEMI patients undergoing primary PCI, resulting in suboptimal inhibition of platelet aggregation for at least 2 h. Such suboptimal inhibition can be overcome efficiently with abciximab.

Competing Interest

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: support from the Austrian Society of Cardiology for the submitted work; JSM received lecture or consultant fees from Daiichi Sankyo, Eli Lilly and Astrazeneca; RDC received fees, honoraria and research funding from Sanofi-Aventis, Boehringer Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo, Novartis, Merck and Lilly; BJ reported consultant fees and research funding from AstraZeneca and Bayer; GC received lecture or

consultant fees from Daiichi Sankyo and Eli Lilly; IML has relationships with drug companies including AOPOrphan Pharmaceuticals, Actelion, Bayer, Astra-Zeneca, Servier, Cordis, Medtronic, GSK, Novartis, Pfizer and United Therapeutics, in the previous 3 years. In addition, IML is an investigator in trials involving these companies, with relationships including consultancy service, research grants and membership in scientific advisory boards.

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Contributors

JMS-M, JK, DA, RC, GC and IML were responsible for the study conception. JMS-M and IML designed the study. SS was responsible for patient inclusion, and collection of laboratory and patient data; JMS-M analysed the data. JMS-M, JK, DA, RC, ELH, BJ and GC interpreted the data. All authors were involved in drafting the manuscript, and contributed to revisions of the draft and approval of the final manuscript.

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