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Morphine delays the onset of action of prasugrel in patients with prior history of ST-elevation myocardial infarction

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Summary

Delays in the onset of action of prasugrel during primary percutaneous coronary intervention (PPCI) have been reported and could be related to the effects of morphine on gastric emptying and subsequent intestinal absorption. The study objective was to determine whether morphine delays the onset of action of prasugrel in patients with a prior history of ST-elevation myocardial infarction (STEMI) treated with PPCI. This was a crossover study of 11 aspirin-treated patients with prior history of STEMI treated with PPCI, for which prasugrel and morphine had been previously administered. Patients were randomised to receive either morphine (5 mg) or saline intravenously followed by 60 mg prasugrel. Blood samples were collected before randomised treatment and over 24 hours after prasugrel administration. The inhibitory effects of prasugrel on platelets were determined using the VerifyNow P2Y12 assay and light transmission aggregometry. Plasma levels of prasugrel and prasugrel active metabolite were measured. Platelet reactivity determined by VerifyNow PRU, VerifyNow % Inhibition and LTA was significantly higher at 30–120 minutes (min) when morphine had been co-administered compared to when saline had been co-administered. Morphine, compared to saline, significantly delayed adequate platelet inhibition after prasugrel administration (158 vs 68 min; $p = 0.006$). Patients with delayed onset of platelet inhibition also had evidence of delayed absorption of prasugrel. In conclusion, prior administration of intravenous morphine significantly delays the onset of action of prasugrel. Intravenous drugs may be necessary to reduce the risk of acute stent thrombosis in morphine-treated STEMI patients undergoing PPCI.

Keywords

Prasugrel, $P2Y_{12}$ inhibitors, antiplatelet medications, morphine, platelet reactivity

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Introduction

Emergency reperfusion by primary percutaneous coronary intervention (PCI) is the standard of care for patients with ST-elevation myocardial infarction (STEMI) (1). Rapid and potent adjunctive antiplatelet therapy is necessary to prevent periprocedural complications such as stent thrombosis. Increasingly this has been achieved with platelet $P2Y_{12}$ inhibitors in combination with aspirin. Successive strategies have involved clopidogrel, higher doses of clopidogrel and, more recently, prasugrel and ticagrelor (2).

A major limitation of clopidogrel is its relatively slow onset of action, as it is a pro-drug that requires conversion into its active metabolite in two steps by hepatic cytochrome P450 (CYP) enzymes (3). In contrast, prasugrel is converted into its intermediate form by plasma esterases and requires only one CYP-mediated conversion (4). Although the active metabolites of clopidogrel and prasugrel are very similar, the more efficient metabolism of prasugrel results in more rapid and consistent generation of its active metabolite (4). Accordingly, prasugrel achieves faster and more potent $P2Y_{12}$ inhibition than clopidogrel (5, 6) and thereby reduces the risk of adverse cardiovascular events in patients with STEMI undergoing PCI (7, 8).

In healthy volunteers, prasugrel potently inhibits platelet aggregation within 30–60 minutes (min) (5). However, for reasons that are not fully understood, prasugrel does not achieve potent platelet inhibition until up to approximately 4 hours (h) after its administration to patients with acute coronary syndromes acute coronary syndrome (ACS) (9). Multivariate analysis of clinical studies has suggested that morphine, which is often administered to patients with STEMI, is associated with a delayed onset of action of prasugrel (9, 10), although it has not yet been demonstrated whether this relationship is causal. As morphine is known to delay gastric

emptying and onset of action of drugs that rely on intestinal absorption (11), we therefore hypothesised that morphine may delay and reduce the effect of prasugrel, which is dependent on intestinal absorption (12).

Materials and methods

Study design

This open-label, cross-over study was approved by a National Health Service (NHS) Research Ethics Committee (UK) and the Medicines and Healthcare products Regulatory Agency (UK) and conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All subjects provided written, informed consent. The study was registered at http://www.clinicaltrials.gov (unique identifier NCT01536964).

Study population

Patients were recruited if they had been admitted to hospital for STEMI more than 12 months previously and had been treated with prasugrel and morphine for their STEMI with no adverse effects. Inclusion criteria also included age between 18 and 75 years of age, postmenopausal if female and weight over 60 kg. Exclusion criteria included active respiratory disorders, decompensated heart failure, current use of any antiplatelet medications other than aspirin within the last two weeks, current use of opiate analgesia, any condition that confers an increased risk of bleeding, active liver disease, anaemia or thrombocytopenia.

Experimental protocol

Twelve subjects were randomised to receive either 5 mg morphine or saline intravenously given in two divided doses 10 min and 5 min before the administration of a 60 mg prasugrel loading dose. After a washout period of 3–4 weeks, patients then crossed over and received saline if they had previously received morphine or received morphine if they had previously received saline (▶Figure 1). A venous cannula was inserted into an antecubital vein in each arm. One cannula was used for blood sampling and the other for administration of morphine. Venous blood samples were collected at baseline (prior to saline or morphine), before prasugrel administration and at the following timepoints after prasugrel administration: 0.5, 1, 2, 4, 6 and 24 h.

Pharmacodynamic measurements

Blood was collected into tubes containing trisodium citrate dihydrate (3.13% w/v) for measurement of platelet aggregation. The VerifyNow P2Y12 assay (Accumetrics Inc, San Diego, CA, USA)

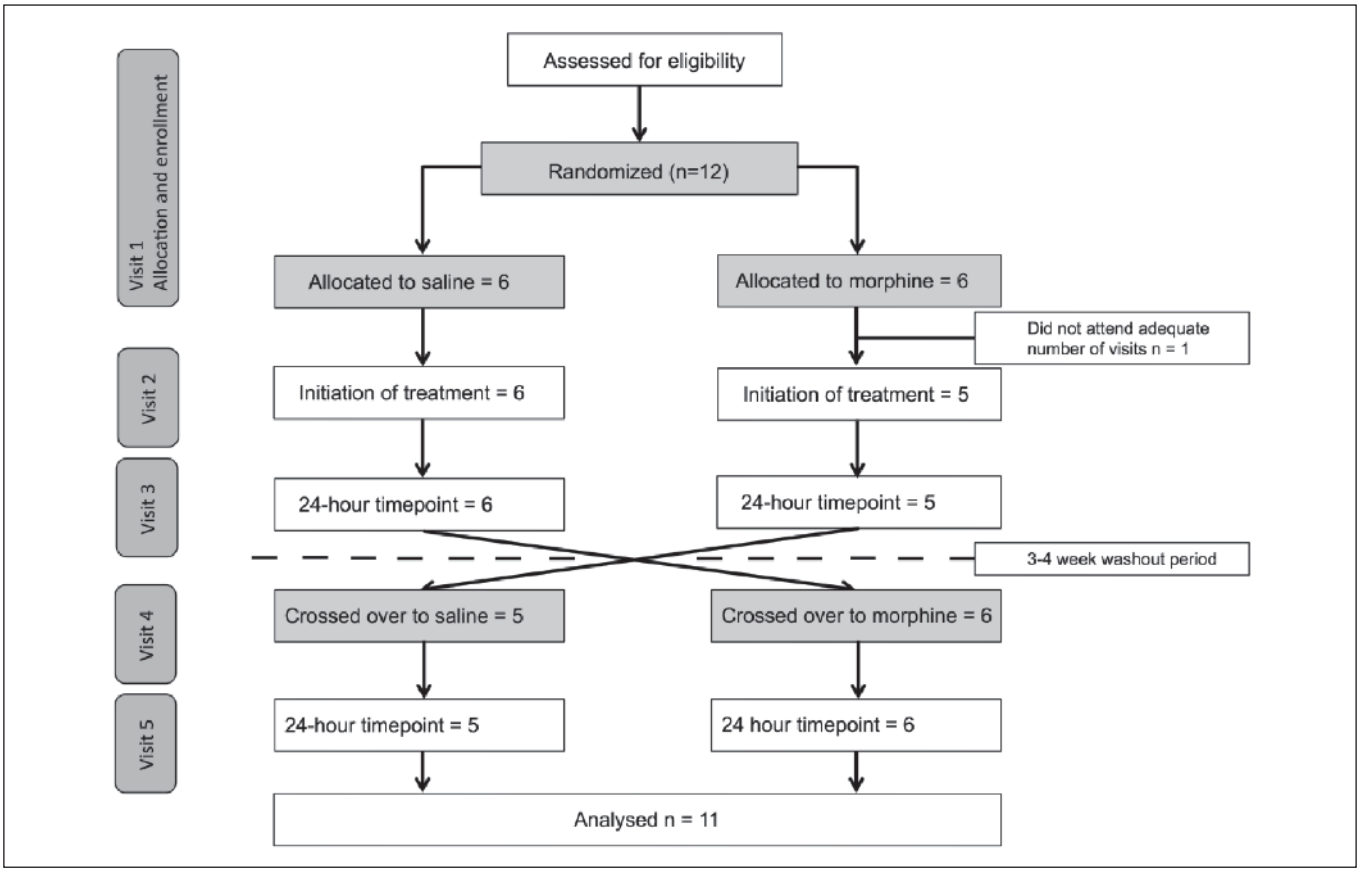

Figure 1: Study design and patient recruitment.

was performed after 20 min according to the manufacturer's instructions. Platelet-rich plasma (PRP) was prepared by centrifugation of whole blood at 200 g for 10 min at room temperature and removal of supernatant. Platelet aggregation induced by 20 μM adenosine diphosphate (ADP) was assessed in PRP by light transmission aggregometry (LTA) using a BioData PAP-8E optical aggregometer (BioData, Horsham, PA, USA). Maximum and final platelet aggregation after 6 min were recorded.

Pharmacokinetic measurements

Blood was collected into chilled tubes containing EDTA 4 mmol/l and 50 μl of 500 mmol/l 3-methoxyphenacylbromide (MPB), which binds to the reactive thiol group of prasugrel's active metabolite to create a stable derivative. Samples were placed on ice and centrifuged for 10 min at 1500 g followed by removal of supernatant plasma that was stored at –80 °C prior to analysis. Analysis was performed by ABSciex QTRAP4000 LC/MS/MS system from Applied Biosystems (Applied Biosystems, Foster City, CA, USA) using prasugrel and the MPB derivative of prasugrel's active metabolite (ALSACHIM Bioparc, Illkirch Graffenstaden, France) as standards for calibration.

Endpoints

The primary endpoint was the VerifyNow P2Y12 PRU value at 2 h after administration of prasugrel. Secondary endpoints included estimated time to achieve a PRU value of less than 208 (a threshold previously identified as a cut-off for high platelet reactivity [13, 14]), VerifyNow % inhibition, platelet aggregation determined by LTA and plasma concentrations of prasugrel and prasugrel active metabolite. It was calculated that a crossover design with a sample size of 12 would have over 80 % power to detect an effect size of 0.25 with an alpha of 0.05, allowing for drop-out of one patient before the final study visit.

Table 1: Baseline characteristics of patients receiving saline and morphine (cross over design).

Variable	Value
Age (years – median [IQR])	64 (59–66)
Male sex (%)	11/11 (100 %)
Caucasian race	11/11 (100 %)
Hyperlipidaemia (%)	6/11 (55 %)
Hypertension (%)	6/11 (55 %)
Diabetes mellitus (%)	2/11 (18 %)
Smoking (%)	5/11 (45 %)
Prior transient ischaemic attack	0/11 (0 %)
Prior stroke	0/11 (0 %)
Peripheral vascular disease (%)	1/11 (9 %)
History of angina	3/11 (27 %)
Prior ST-elevation myocardial infarction (%)	11/11 (100 %)
Prior PCI (%)	11/11 (100 %)
Chronic kidney disease	0/11 (0 %)
Statin use (%)	10/11 (91 %)
Ace inhibitor use (%)	9/11 (82 %)
Beta blocker use (%)	6/11 (55 %)

Statistical analysis

Continuous data are expressed as mean ± standard error of the mean (SEM) or medians (interquartile range) as appropriate. Categorical data are expressed as proportions (%). Pharmacodynamic and pharmacokinetic parameters were analysed separately using a mixed effect linear model with patient as a random effect, treatment as a fixed effect and baseline values as covariates. Statistical significance was considered for two-sided p-values <0.05. Statistical analyses were performed using SPSS for Mac (version 20.0 IBM Corp, Armonk, NY, USA) and GraphPad Prism version 6 (GraphPad Software Inc, La Jolla, CA, USA).

Results

Baseline characteristics

Eleven patients completed the study and one patient did not attend for his visits after completing screening and enrolment so could not be included in the analyses (►Figure 1). The median age was 64 years and all patients had a history of STEMI more than 12 months and less than three years previously that had been treated with prasugrel and morphine (►Table 1).

VerifyNow P2Y12 assay results

The primary endpoint of VerifyNow PRU at 2 h after prasugrel loading dose was significantly higher with morphine co-administration than with saline co-administration (104 ± 33 vs 26 ± 11; p < 0.001; ►Figure 2). Platelet reactivity, as determined by VerifyNow PRU, was significantly higher from 30 min up to 2 h after prasugrel loading dose when morphine had been co-administered compared to when saline had been co-administered (all p < 0.01; ►Figure 2A). VerifyNow % inhibition showed the same pattern of effect of morphine at 30–120 min post prasugrel loading dose (all p < 0.01; ►Figure 2B). Consequently morphine, compared to saline, significantly increased the estimated time to achieve adequate platelet inhibition (VerifyNow P2Y12 PRU value < 208 [13]) after prasugrel administration (158 vs 68 min; p = 0.006). No patients had HPR at 2 h when saline was co-administered, whereas three patients still had HPR when morphine was co-administered.

Light transmission aggregometry

This adverse effect of morphine on onset of pharmacodynamic response to prasugrel was also confirmed using LTA. Platelet reactivity, as determined by maximal and final aggregation responses,

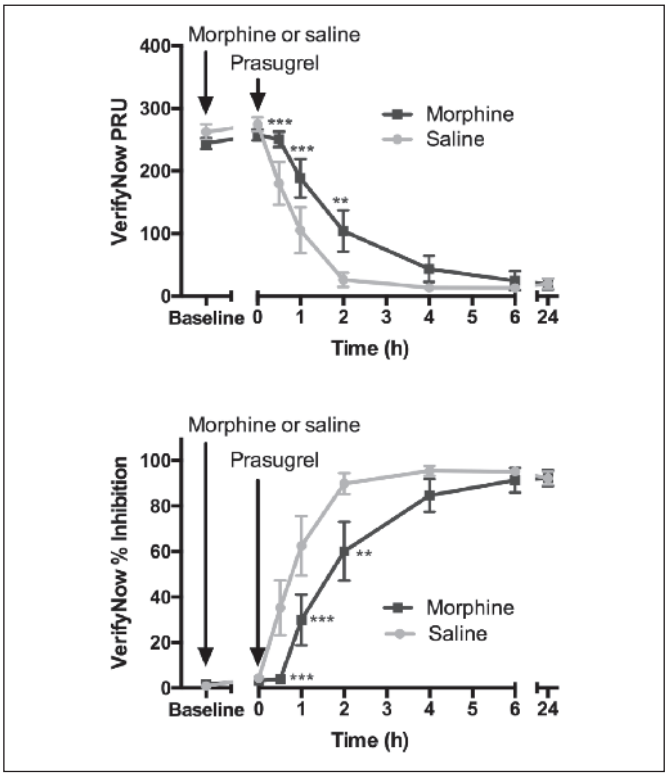

Figure 2: VerifyNow $P2Y_{12}$ PRU values (A) and VerifyNow % Inhibition (B) before (t = 0 h) and after administration of prasugrel in patients pre-treated with either morphine or saline (crossover design, n=11). Effect of morphine, compared to saline, determined by a linear mixed effects model with Bonferroni correction for multiple comparisons (*p<0.05, **p<0.01 and ***p<0.001).

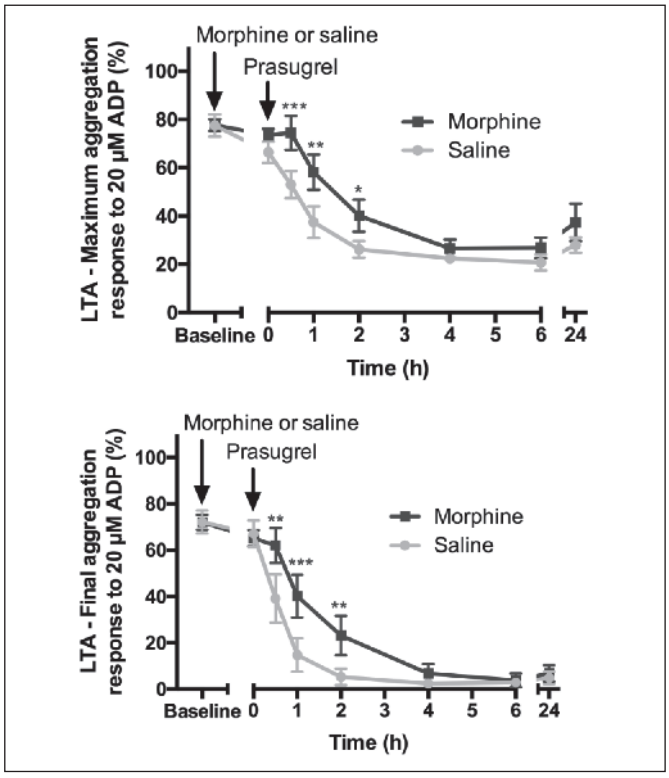

Figure 3: Light transmission aggregometry (LTA) – maximum aggregation induced by 20 µM ADP (A) and final aggregation induced by 20 µM ADP (B) before (t = 0 h) and after administration of prasugrel in patients pre-treated with either morphine or saline (crossover design, n=11). Effect of morphine, compared to saline, determined by a linear mixed effects model with Bonferroni correction for multiple comparisons (*p<0.05, **p<0.01 and ***p<0.001).

was significantly higher at 30–120 min when morphine had been co-administered compared to when saline had been co-administered (all $p < 0.05$; ▶Figure 3). At 2 h, mean platelet aggregation responses were significantly higher with morphine co-administration than with saline co-administration (maximum aggregation 40 % ± 7 vs 26 % ± 3 [p = 0.01; ▶Figure 3A] and final aggregation 23 % vs 5 % [p = 0.001; ▶Figure 3B]).

Pharmacokinetics

Overall there were no significant effects of morphine administration on pharmacokinetic parameters (▶Table 2). However, when selectively assessing the subgroup of five patients who had morphine-associated delay in onset of pharmacodynamic response at 2 h, as assessed by VerifyNow, there was evidence of delayed absorption of prasugrel (▶Figure 4). In these patients, levels of prasugrel active metabolite were significantly lower at 30 min when morphine had been co-administered compared to when saline had been co-administered (5 vs 120 ng/ml; p = 0.026; ▶Figure 4C). Plasma levels of the parent prasugrel compound were also numerically lower at 30 min when morphine was co-administered, compared to when saline was co-administered, but this was not statistically significant when assessed by a linear mixed effects model (0.000 vs 0.022 ng/ml; p = 0.51; ▶Figure 4B).

Discussion

Rapid and potent platelet inhibition is required at the time of primary PCI for STEMI in order to prevent periprocedural complications such as stent thrombosis. Although prasugrel achieves potent platelet inhibition within approximately 30–60 min in healthy volunteers (6), its effects can be delayed by up to 6 h or more in patients with STEMI, for reasons that are incompletely understood (9, 15). Since morphine delays gastric emptying and subsequent intestinal drug absorption (11), we investigated whether morphine adversely affects response to prasugrel.

The main finding of our study was that morphine delays the onset of action of prasugrel by approximately 90 min on average in patients with a prior history of STEMI. In some cases, adequate platelet inhibition is not achieved until 4–6 h after prasugrel administration when morphine has been co-administered. In those patients who had a delay in pharmacodynamic response caused by

	Saline	Morphine	P-value
Prasugrel C_{max} (ng/ml)	0.11 ± 0.03	0.08 ± 0.02	0.41
Prasugrel T_{max} (min)	100 ±19	114 ± 24	0.54
Prasugrel AUC (ng/ml x h)	0.70 ± 0.41	0.26 + 0.12	0.17
Prasugrel active metabolite C_{max} (ng/ml)	287 ± 36	324 ± 93	0.66
Prasugrel active metabolite T_{max} (min)	71 ± 12	95 ± 19	0.17
Prasugrel active metabolite AUC (ng/ml x h)	1123 ± 412	1038 ± 248	0.77

Table 2: Pharmacokinetics.

morphine, there was a significant reduction in plasma levels of prasugrel active metabolite at 30 min.

A recent study demonstrated that morphine delays the onset of action of clopidogrel in healthy volunteers (16). For the first time, our study proves that morphine also delays the effects of antiplatelet medications in patients with a prior history of STEMI and that even the more potent $P2Y_{12}$ inhibitor, prasugrel, is not able to overcome this effect. This is supported by the findings of post-hoc multivariate analysis of clinical studies, which shows an association between morphine use and a reduced response to prasugrel (10). The effect of morphine does not appear to be limited to the thienopyridine $P2Y_{12}$ inhibitors, clopidogrel and prasugrel, since morphine is also associated with a delayed onset of action in patients treated with ticagrelor (10, 17). The Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) study sought to demonstrate whether ambulance administration of ticagrelor improved reperfusion in patients with STEMI compared to administration in-hospital (18). This study failed to show overall benefit of pre-hospital treatment with ticagrelor but there was a suggestion of enhanced reperfusion in those patients receiving pre-hospital ticagrelor who did not receive morphine. Consistent with this observation, pharmacodynamic data showed that morphine treatment was associated with markedly delayed onset of action of ticagrelor in the ATLANTIC pharmacodynamics substudy (19). In addition, it has recently been shown that morphine reduces exposure to ticagrelor and its active metabolite, which is associated with a reduced action of ticagrelor in patients with MI (20). It is therefore likely that the benefit of earlier ticagrelor administration was nullified by co-administration of morphine.

Large observational studies have shown that some morphine-treated patients have rapid onset of action of prasugrel, whereas others have a delayed onset of action (9, 15). Our overall study population did not show a significant effect of morphine on pharmacokinetic parameters, but there was evidence of delayed pharmacokinetics specifically in the subset of patients with delayed pharmacodynamic response following morphine. This is consistent with delayed intestinal absorption in these patients, thereby providing a mechanistic explanation for the delay in onset of

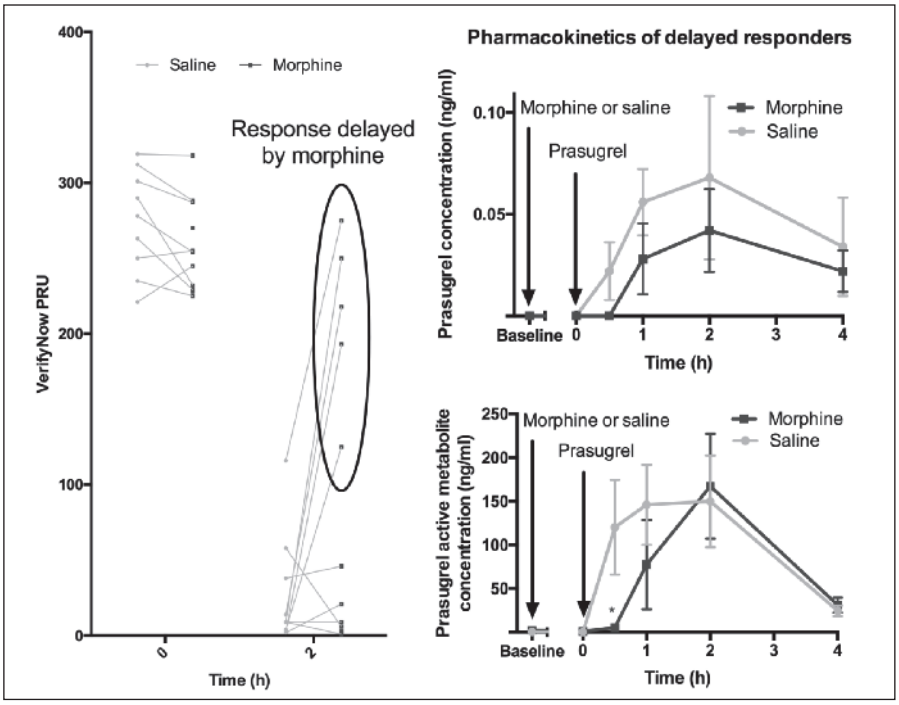

Figure 4: Delayed pharmacodynamic response (A) and plasma levels of prasugrel (B) and prasugrel active metabolite (C) before (t = 0 h) and after administration of prasugrel in patients pre-treated with either morphine or saline. VerifyNow PRU (A; n=11) demonstrated delayed response in five patients and the pharmacokinetics of these patients are shown in B and C. Effect of morphine, compared to saline, determined by a linear mixed effects model with Bonferroni correction for multiple comparisons (*p<0.05, **p<0.01 and ***p<0.001).

action of prasugrel in these patients. It is likely that no significant overall difference was seen in the pharmacokinetic parameters because the delay only occurred in a relatively small subgroup. Further work is needed to determine why morphine only delays the onset of action of prasugrel in a subset of patients. During acute MI, platelets become activated, many bioactive substances are released systemically including catecholamines that may increase platelet reactivity, and other additional medications are administered. Changes in autonomic nervous system activity related to acute MI might also affect gastric emptying and intestinal motility. Further work is therefore also needed to determine whether these factors may contribute to the delayed response to prasugrel that is seen in patients with acute MI.

Administration of titrated intravenous opioids to relieve pain is currently recommended for the management of STEMI (1). However, it has been shown that morphine use is associated with an increased risk of mortality in patients with non-ST-elevation ACS, even if baseline risk is adjusted for (21). The findings of our study suggest that morphine should only be administered prior to administration of prasugrel if strictly necessary to control pain or distress. In the event that morphine has been administered, parenteral use of antiplatelet agents such as GPIIb/IIIa antagonists may be required to prevent acute stent thrombosis during the time that it takes for morphine's effects to wear off. At present, there is no direct evidence to suggest alternatives to the use of morphine for patients with STEMI who are in need of analgesia. Ongoing clinical trials are aiming to determine whether fentanyl has less of an effect on the absorption of $P2Y_{12}$ inhibitors than morphine (clinicaltrials.gov reference NCT02531165). However, delayed gastric emptying is a class effect of opioid-based analgesia and it is therefore likely that alternative strategies such as non-opioid analgesia will be needed in order to avoid delayed absorption of oral $P2Y_{12}$ inhibitors.

Limitations

Randomising morphine vs placebo would be ethically problematic in patients with current STEMI. We therefore investigated patients with a prior history of STEMI who no longer required treatment with a $P2Y_{12}$ inhibitor, but the effects of morphine may be even further exacerbated by gastroparesis in patients with ongoing myocardial ischaemia and associated autonomic disturbance.

Conclusions

Prior administration of intravenous morphine significantly delays the onset of platelet inhibition following oral administration of a prasugrel loading dose.

Acknowledgements

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What is known about this topic?

- Delays in the onset of action of prasugrel have been reported in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction.
- Morphine delays gastric emptying and subsequent intestinal absorption, which may delay the absorption of prasugrel.

What does this paper add?

- This study establishes that morphine delays the onset of action of prasugrel.
- Further, there is evidence of delayed absorption in morphine-treated patients with a delayed onset of action of prasugrel.
- This suggests that morphine-treated patients undergoing primary percutaneous coronary intervention may require intravenous drugs to reduce the risk of stent thrombosis.

Conflicts of interest

R. Storey reports institutional grants from AstraZeneca; research support from Accumetrics; honoraria from AstraZeneca, Accumetrics, and Medscape; consultancy fees from AstraZeneca, Correvio, Accumetrics, The Medicines Company, Aspen, PlaqueTec and Thermo Fisher Scientific. None of the other authors reports any conflicts of interest.

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