

# Temporary and reversible clopidogrel, ticagrelor and prasugrel high on-treatment platelet reactivity associated to the concomitant use of morphine and fentanyl in acute coronary syndrome

## Abstract

**Background:** Recent evidence demonstrates that morphine significantly reduces absorption and delays onset of action of P2Y12-receptor inhibitors in patients with acute coronary syndrome.

**Case summary:** 55-year-old male with inferior ST-segment-elevation myocardial infarction was treated with opioids previous and during primary angioplasty, developing temporary and reversible clopidogrel, ticagrelor and prasugrel high on-treatment platelet reactivity assessed by platelet function test. We treated with glycoprotein IIb/IIIa inhibitor as a bridge to obtain antiplatelet effect by P2Y12-receptor inhibitors.

**Discussion:** The interaction between opioids and oral P2Y12-receptor inhibitors in patients with acute coronary syndrome should be highlighted. Although morphine administration may potentially lead to detrimental clinical consequences by diminish of antiplatelet effect, its routine avoidance cannot be recommended until large scale trials be available. We suggest that if the use of morphine and other opioids is inevitable, utilization of platelet function tests to guide the antiplatelet treatment is an option.

**Keywords:** ticagrelor, morphine, high on-treatment platelet reactivity, P2Y12-receptor inhibitors, case report

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**Abbreviations:** PCI, percutaneous coronary intervention; ACS, acute coronary syndrome; HTPR, high on-treatment platelet reactivity; ST, elevation myocardial infarction. LD, loading dose; PCI, percutaneous coronary intervention; VN, Verify Now; PRU, platelet reaction unit; IPA, inhibition of platelet aggregation; ARU, aspirin reaction units; MD, maintaining dose

## Introduction

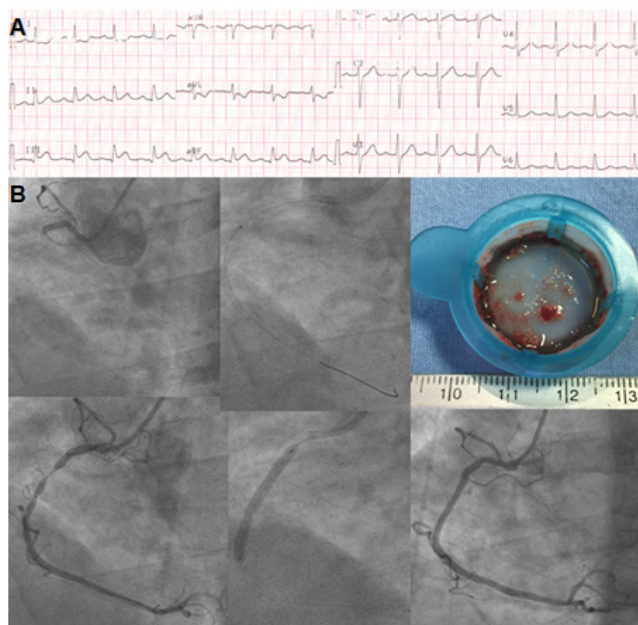
There is accumulating data demonstrating a link between high on-treatment platelet reactivity (HTPR) and atherothrombotic complications in patients presenting with acute coronary syndrome (ACS) or following percutaneous coronary intervention (PCI).<sup>1</sup> Recent evidence demonstrates that morphine and opioids significantly reduce absorption and delays onset of action of P2Y12-receptor inhibitors in patients with ACS.

Timeline	
Day 1	10:45 hrs. Patient presenting with inferior STEMI 11:00 hrs. Aspirin 300-mg, clopidogrel 300 mg LD and morphine 10-mg IV were administered.
	12:00 hrs. Ticagrelor 180-mg LD was administered.
	12:15 hrs. Primary PCI with implantation of drug-eluting stent in proximal and medium right coronary artery without complications; fentanyl 150-µg IV was used to relief pain.
	13:00 hrs. VN: 250 PRU, 0% IPA; 482 ARU.
	16:00 hrs. VN: 290 PRU, 0% IPA. Second chewed ticagrelor 180mg LD
	20:00 hrs. VN: 232 PRU, 0% IPA. Switch to prasugrel 60mg LD, 10mg MD.
	23:00 hrs. VN: 215 PRU; 0% IPA. High-dose bolus tirofiban during 12hrs was initiated. Prasugrel 10-mg MD.
Day 2	11:00 hrs. tirofiban infusion was stopped. 23:00 hrs. VN: 112 PRU, 36% IPA on prasugrel MD. HTPR was resolved. (36hrs after opioids administration).
Day 3	13:00hrs. VN: 142 PRU, 40% IPA. 423 ARU on prasugrel MD. We received CYP2C19 *2/*2 genetic polymorphism report.
Day 4	13:00hrs. VN: 160 PRU, 16% IPA. Switch to ticagrelor 180-mg LD, 90-mg bid MD.
Day 5	13:00hrs. VN: 120 PRU, 34% IPA on ticagrelor MD. Patient discharged without complications.
Day 12	7:00hrs. VN: 89 PRU; 43% IPA on ticagrelor MD. Patient asymptomatic.
Day 30	7:00 hrs. VN: 55 PRU; 64% IPA on ticagrelor MD. Patient asymptomatic.

**STEMI:** ST-elevation myocardial infarction. **LD:** loading dose. **PCI:** percutaneous coronary intervention. **VN:** Verify Now. **PRU:** platelet reaction unit. **IPA:** inhibition of platelet aggregation. **ARU:** aspirin reaction units. **MD:** maintaining dose.

## Case presentation

55-year-old male with no major coronary risk factors presented with inferior ST-segment–elevation myocardial infarction (STEMI); he was treated with aspirin 300-mg loading dose (LD), clopidogrel 300-mg LD, atorvastatin 80-mg and intravenous morphine 10-mg. One hour later a chewed ticagrelor 180 mg LD was administered. A primary PCI with a single drug eluting stent in the right coronary artery was performed (Figure 1) without complications; during the procedure due to pain, intravenous fentanyl 150- $\mu$ g and midazolam 1-mg was administered.



**Figure 1A** 12-lead surface EKG showing inferior ST-segment elevation.

**Figure 1B** Conventional primary PCI procedure was performed with thrombus aspiration, and DES was implanted

As part of a clinical trial, we performed platelet function test (PFT) using VerifyNow P2Y12/aspirin (Accriva Diagnostics, San Diego, California). Results are expressed in P2Y12 reaction units (PRU) and % inhibition of platelet aggregation (IPA), aspirin results are expressed in aspirin reaction units (ARU). The cutoff associated with high on-treatment platelet reactivity (HTPR) is  $\geq 208$  PRU and/or  $\leq 15\%$  of IPA.<sup>1</sup>

The first PFT—one hour after ticagrelor LD— showed HTPR with 235 PRU and 0% of IPA, but adequate response to aspirin with 482 ARU. Four hours later a new test showed 290 PRU and 0% IPA. As there was no effect neither clopidogrel nor ticagrelor, we administered a second chewed ticagrelor LD. Eight hours after the first ticagrelor LD,—4 hours after the second LD—a new PFT showed persistence of HRPT, with 232 PRU and 0% IPA. We switched to chewed prasugrel 60-mg LD. 11hours after first ticagrelor LD,—7hours after second ticagrelor LD and 3hours after prasugrel LD— VerifyNow showed 215 PRU, and 0% IPA. We initiated intravenous high-dose bolus tirofiban with conventional maintaining dose (MD) during 12hours. Twelve hours after tirofiban interruption PFT showed, 112 PRU with 36% IPA. The day after on prasugrel MD PFT was 142 PRU and

40% IPA. On the fourth day PFT showed 160 PRU and 16% IPA. Because we had attributed the cause of HTPR to the use of morphine and fentanyl, we made a new switch to ticagrelor with 180mg LD and conventional MD. The next day his PFT was 120 PRU and 34% IPA. The patient was discharged with ticagrelor without bleeding or thrombotic events during his hospitalization. One week later platelet reactivity was 89 PRU with 43% IPA. Finally, platelet reactivity at month was 55 PRU with 64% IPA. In addition, genotyping test showed CYP2C19 loss-of-function homozygous  $*2/*2$ , which may be related to a poor metabolism of clopidogrel. No complications was observed during 2,5-year follow-up, and the left ventricle function is normal.

## Discussion

P2Y12–receptor inhibitors, concurrently administered with aspirin are a mainstay of treatment for patients with ACS.<sup>1</sup> Morphine and fentanyl, on the contrary, are a nonessential but commonly used drugs in ACS and during PCI to relieve pain.<sup>2</sup> The guidelines for the management of patients with STEMI recognize that the use of morphine may be associated with a slower uptake, delayed onset of action, and diminished effects of oral antiplatelet agents, which may lead to early treatment failure in susceptible individuals. In any case, the indication persists and intravenous opioids should be used for pain relief, with class IIa indication.<sup>3</sup>

Although evidence on morphine and its potential interactions with P2Y12–receptor inhibitors has been recently informed, the interaction with other opioids is even more unknown. This interaction may result in increased platelet reactivity, and is most possibly because of the inhibitory effect of opioids on gut motility. HTPR for clopidogrel has been widely studied. In comparison, there is little information explaining possible causes of HTPR on ticagrelor treatment, however, it is accepted that it is an infrequent phenomenon.

Stent thrombosis, while on treatment with ticagrelor is rare.<sup>4</sup> There is only two reported cases, to our knowledge, of such event with HTPR demonstrated by platelet function tests.<sup>5,6</sup> A third patient was described in a short cases series, finding HTPR with ticagrelor after its use in a patient with subacute stent thrombosis, the patient did not develop complications in the follow-up.<sup>7</sup> Unfortunately in none of the few published cases, the HTPR mechanisms could be elucidated.

It has been proposed that the main mechanism for morphine-IP2Y12 interaction is the inhibition of gastric emptying, which can result in marked delays in the absorption of orally administered drugs.<sup>8</sup> The activation of the opioid receptors located in the myenteric plexus decreases propulsive motility and secretion of the gastrointestinal tract, resulting in inhibition of gastric emptying, increase in sphincter tone, induction of stationary motor patterns and blockade of peristalsis ensue. This effects are important for all P2Y12–receptor inhibitors.

IMPRESSION trial<sup>9</sup> studied the effect of intravenous morphine 5mg on the pharmacokinetics (PKs) and pharmacodynamics(PDs) profile of 180-mg ticagrelor in 70 patients with STEMI. Morphine was associated with lower total exposure to ticagrelor and its active metabolite AR-C124910XX, with a concomitant delay in maximal plasma concentration of ticagrelor. At 2hours after the loading dose, the proportion of patients with high residual platelet reactivity was 57% in the morphine group versus 29% in controls ( $p=0.03$ ).<sup>9</sup>

PACIFY, studied patients undergoing clinically-indicated coronary angiography with or without fentanyl. Platelet reactivity was higher in fentanyl-treated patients 2 hours after administration of a regular ticagrelor formulation in patients undergoing elective PCI.

PACIFY demonstrates that fentanyl administration lowers plasma concentrations of ticagrelor and delays its antiplatelet effects. The results extend previous studies reporting that morphine delays the absorption and effects of P2Y<sub>12</sub> inhibitors.<sup>10</sup>

Recently, METAMORPHOSIS trial<sup>11</sup> investigate whether metoclopramide co-administration could reduce delay and improve the PKs and PDs of ticagrelor and AR-C124900XX in patients with ACS treated with morphine. Mean platelet activity within the first hour was noticeably higher in metoclopramide-naive patients. Moreover, ticagrelor plasma concentration was significantly higher in patients receiving metoclopramide, they conclude, the co-administration of metoclopramide in ACS patients and treated with morphine, has a beneficial effect on the PKs/PDs profile of ticagrelor and its metabolite.<sup>11</sup>

Our case must be evaluated in light of some controversial issues. First, the use of GP IIb-IIIa inhibitors (GPI) should have been earlier, although at that time we did not have it, therefore the delay of 7 hours in its administration. In fact, the evidence of adverse effects of morphine in patients with STEMI, included: enhanced platelet reactivity and impaired endogenous fibrinolysis, reduced occurrence of spontaneous reperfusion pre-primary PCI and non-independently associated with larger infarct size, and may be favorably influenced by upfront GPI administration in the early stages of STEMI.<sup>12</sup>

Second, the double LD of ticagrelor, in a study in patients with STEMI undergoing primary PCI, doubling the LD of ticagrelor was not accompanied by a faster than standard dose onset of antiplatelet action;<sup>13</sup> however, in non-ST-segment elevation, the APELOT trial, doubling the ticagrelor LD achieved faster onset and greater platelet inhibition without an increase in adverse events.<sup>14</sup> We tried to overcome the HTPR using a second LD of ticagrelor, while we got the GPI, being aware that it is an off-label indication. The double dose and the change of P2Y<sub>12</sub>-inhibitors were not useful to overcome the HTPR. Cangrelor was no option, because it is not marketed in our country.

Third, although there were no clinical endpoints related to the state of platelet function, it is very difficult to determine the clinical evolution if we had not performed PFT, however, in the clinical context of STEMI, it is desirable to have an early and effective antiplatelet response.

Finally, we must emphasize that PFT are not recommended for routine use; in this case the patient was included in a pharmacodynamic research trial, so that the Verify Now was requested per-protocol.

## Conclusions

We demonstrated HTPR and PDs delay action of clopidogrel, ticagrelor and prasugrel in the same patient after concomitant use of opioids drugs before and during a primary PCI in ACS and finally that after 36 hours recover the antiaggregant effect of the P2Y<sub>12</sub>-receptor inhibitors. In addition, the CYP2C19 loss-of-function allele \*2/\*2 could have played a relevant role in the inadequate response to clopidogrel, although irrelevant to the metabolism of prasugrel and ticagrelor.

Probably, the use of opioids during an ACS should be avoided as much as possible, but if its requirement is indispensable, PFT to guide antiplatelet therapy become a useful and effective strategy. In our opinion, this case illustrates the rational use of these in the setting of an ACS. The treatment options have already been addressed and included strategy like to the metamorphosis trial and use of GP IIb/IIIa inhibitors

## Lead author biography

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## Conflicts of interest

Author declare there are no conflicts of interest towards this article.

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