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Review

Impact of morphine on antiplatelet effects of oral P2Y12 receptor inhibitors

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ABSTRACT

Morphine and P2Y12 receptor inhibitors are both recommended in patients with acute myocardial infarction. Morphine may impede gastrointestinal absorption of several oral drugs including P2Y12 platelet receptor inhibitors.

The aim of this review was to critically discuss drug–drug interactions between oral P2Y12 receptor inhibitors and morphine according to currently available knowledge based on the findings of experimental, observational and randomized clinical studies.

The morphine–clopidogrel pharmacodynamic interaction has been observed in numerous trials and it has been proposed as an explanation for the negative impact of morphine on the clinical outcomes in patients with acute coronary syndromes. An analogous morphine interaction with ticagrelor and prasugrel was found in several observational studies and finally proven in randomized trials in healthy volunteers and acute myocardial infarction patients.

Morphine delays and attenuates exposure and antiplatelet action of oral P2Y12 receptor inhibitors in patients with myocardial infarction. Although this interaction may have potentially harmful consequences, routine avoidance of morphine cannot be recommended until clinically powered trials are completed.

1. Background

Dual antiplatelet treatment with one of the P2Y12 receptor inhibitors and aspirin is a pivotal therapy in patients with acute coronary syndromes (ACS) [1–4]. According to the current guidelines ticagrelor and prasugrel are preferred in ACS patients undergoing percutaneous coronary intervention (PCI) [3,4].

The rationale for morphine use in patients with acute ischemic chest pain is an expected favorable disease modification [5–7]. The current guidelines for the management of patients with acute myocardial infarction (AMI) continue to recommend intravenous (IV) morphine as the drug of choice for pain relief [3,4]. However, there have never been any randomized clinical trials evaluating the efficacy and safety of morphine in this population, so this recommendation is based solely on expert consensus, not on clinical trial evidence.

Moreover, due to its pharmacological properties, particularly its impact on the gastrointestinal tract, morphine may impede absorption of several orally administered drugs including P2Y12 platelet receptor inhibitors [8].

The aim of this review was to critically discuss drug–drug interactions between oral P2Y12 inhibitors and morphine according to currently available knowledge based on the findings of experimental as well as observational and randomized clinical studies. A search was conducted by two independent investigators (J.K. and A.K.) using PubMed, CENTRAL and Google Scholar databases. No time or language limitations were applied. Proceedings from the Scientific Sessions of the American College of Cardiology (http://www.acc.org), American Heart Association (http://www.heart.org), European Society of Cardiology (http://www.

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escardio.org) were also considered. The following keywords were applied: "morphine" and "clopidogrel", "morphine" and "prasugrel", "morphine" and "ticagrelor", "morphine" and "P2Y12 inhibitors". References of retrieved studies were searched manually for additional studies and reviews.

2. Morphine

The history of opioids is thousands years long. In 1806 Sertürner isolated a pharmacologically active ingredient from a plant and named it morphine after the god of dreams in Greek mythology, Morpheus [9].

The affinity of opioids to G-protein coupled receptors (opioid receptors μ, κ, δ, and opioid receptor like-1 mediating distinctive actions), with subsequent activation of endogenous pain-modulating systems is responsible for the biological effects of morphine [10].

Despite expected relieve of pain and anxiety, morphine also has several potentially harmful side effects. It may cause hypotension, tachycardia as well as bradycardia and respiratory depression [11–13].

The activation of the opioid receptors located in the myenteric plexus and the intestines decreases propulsive motility and secretion of the gastro-intestinal tract. As a result, inhibition of gastric emptying, increase in sphincter tone, induction of stationary motor patterns and blockade of peristalsis ensue [14]. Moreover, nausea and vomiting are also common side effects of morphine (Fig. 1) [6].

Several authors reported impact of morphine on myocardial infarction size [15–19]. In an experimental study, morphine administration before coronary artery occlusion in rats was associated with an increase in myocardial infarction size as assessed by histological techniques 48 h later (45.8% of left ventricular area vs. 35.3%, $p < 0.05$) [15]. On the other hand, an experiment performed on isolated rat hearts showed that morphine given at early reperfusion resulted in a decrease in infarct volume compared to control (9.8 ± 2.5% vs. 30.0 ± 3.7%, $p < 0.001$) [16]. This may be related to the mechanism described by Jang et al. who revealed that activation of the opioid δ receptor results in a cardioprotective effect, by inhibition of mitochondrial permeability transition pore opening [17].

In a single center randomized study the addition of morphine infusion to remote ischemic conditioning (RIC) in ST-segment elevation myocardial infarction (STEMI) patients was associated with a greater percentage of ST-segment resolution and lower peak troponin I levels as compared with RIC alone [18]. These results suggestive of a potentially important role of morphine in ischemic conditioning were supported by observations indicating that the cardioprotective action of ischemic pre-conditioning is blocked by pre-treatment with the opiate receptor blocker naloxone [19]. Nevertheless, studies confirming beneficial clinical effects of morphine in patients with myocardial infarction are lacking. On the contrary, in the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation of the ACC/AHA guidelines) registry use of morphine either alone or in combination with nitroglycerin for patients presenting with non-ST-segment elevation acute coronary syndromes (NSTE ACS) was associated with higher mortality even after risk adjustment and matching on propensity score for treatment [20]. However, the impact of morphine on short- and long-term prognosis in ACS patients still remains ambiguous [21].

3. Morphine and clopidogrel

In the CRUSADE registry out of 57,039 high-risk patients with NSTE ACS treated with clopidogrel, 17,003 (29.8%) patients received morphine within the first 24 h following hospital presentation [20]. The rates of adverse clinical outcomes were higher in patients who received IV morphine as compared with those who did not. The rate of myocardial infarction was 3.8% vs. 3.0%, death 5.5% vs. 4.7%, and the composite end point of death or myocardial infarction was 8.5% vs. 7.1%. After adjustment for differences in baseline characteristics, the rates of all measured end points, including myocardial infarction (adjusted odds ratio [OR] 1.34, 95% CI 1.22–1.48), death (adjusted OR 1.48, 95% CI 1.33–1.64), and the composite end point of death or myocardial infarction (adjusted OR 1.44, 95% CI 1.34–1.56), remained significantly higher in patients who received IV morphine. The risk of mortality was consistently higher across all measured subgroups and

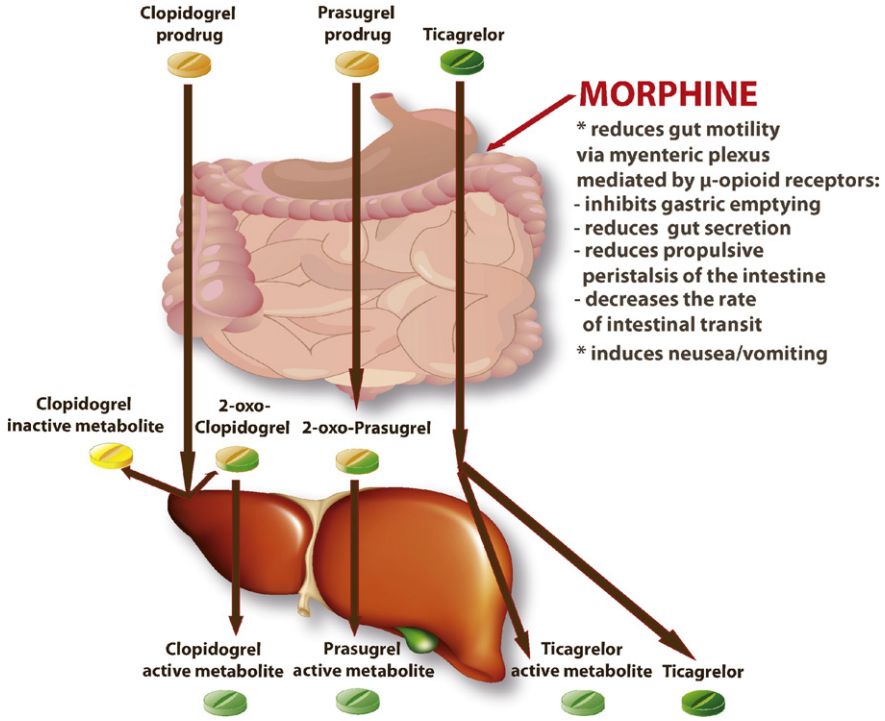

Fig. 1. The possible route of interaction between morphine and P2Y12 receptor inhibitors.