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RECURRENT THROMBOSIS OF THE STENT DUE TO HIGH-DOSE OMEPRAZOLE IN A PATIENT ON DUAL ANTIPLATELET THERAPY WITH CLOPIDOGREL: A CASE REPORT

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Abstract: The case of a 76-year-old woman who consulted the emergency room for angina of four hours of evolution and an episode of hematemesis which had also occurred the previous week is presented. She was admitted with tachycardia, hypertension, and mucocutaneous pallor. The electrocardiogram on admission showed ST depression in the lateral and inferior wall, the initial troponin was negative with a positive control, and the complete blood count showed severe anemia without involvement of the other cell lines. Management was started with omeprazole in continuous infusion for 72 hours and two units of red blood cells were transfused. Subsequently, a digestive endoscopy was performed, which showed a bleeding Dieulafoy lesion that was treated with sclerotherapy. One week later, she underwent coronary angiography with stent implantation in the left anterior descending artery, and dual antiplatelet therapy with aspirin and clopidogrel was started. After the procedure, she had new episodes of angina and required two coronary angiograms that demonstrated acute and recurrent thrombosis in the stent of the intervened artery, with failed interventions, development of cardiogenic shock, and finally death.

Clinical relevance: We present the case of a patient with concomitant use of high-dose intravenous omeprazole and clopidogrel. Possible interactions between these two drugs that may have contributed to the adverse outcomes in the patient are discussed.

Keywords: clopidogrel, omeprazole, stent, thrombosis, proton pump inhibitor, case report.

INTRODUCTION

Dual antiplatelet therapy (DAPT) with acetylsalicylic acid (ASA) and a P2Y12 inhibitor is the standard management of patients with acute coronary syndrome (ACS) to prevent thrombotic events; however, this therapy is associated with an increased risk of bleeding. International guidelines currently recommend the use of clopidogrel over other drugs in its group in combination with proton pump inhibitors (PPIs) in patients with high or very high risk of bleeding, since it has greater gastrointestinal safety (Bouziana, 2015; Collet et al, 2020).

The prescription of PPIs together with clopidogrel remains controversial due to potential drug interactions, particularly with omeprazole (Bouziana, 2015). Clopidogrel is a prodrug that requires hepatic activation by oxidation through the CYP2C19 enzyme, and omeprazole is metabolized by this same enzyme (Li, Andersson, Ahlström, & Weidolf, 2004). The competitive inhibition of CYP2C19 by this drug interaction leads to a decrease in the antiplatelet effect of clopidogrel that has been shown in pharmacokinetic and pharmacodynamic studies (Angiolillo et al., 2011), however clinical studies have shown conflicting results. Studies such as PRINCIPLE–TIMI 44 and PACA support the negative impact of this interaction on the antiplatelet effect, while others such as TRITON TIMI-38 and CREDO did not demonstrate this relationship (Cuisset et al., 2009; Drepper, Spahr, & Frossard, 2012; O'Donoghue et al., 2009; Tentzeris et al., 2010). To date, the only randomized study carried out with 3873 patients that compared the use of omeprazole versus placebo with clopidogrel (COGENT trial) did not show an increase in thrombotic risk, however, the study was terminated prematurely, ischemic events were few compared to those projected for the time of the study and in addition to this, the results presented wide confidence intervals with P values that were not statistically significant (Bhatt et al., 2010). A meta-analysis published in 2017 demonstrated a significantly increased risk of stent thrombosis with the

concomitant use of clopidogrel with proton pump inhibitors, although another published in 2019 did not demonstrate an increase in cardiovascular outcomes in patients using PPIs. and DAPT (Bundhun, Teeluck, Bhurtu, & Huang, 2017; Khan et al., 2019). A meta-analysis was recently published in which it was shown that the use of DAPT together with PPIs increases the risk of major adverse cardiovascular events (MACE) (HR =1.15 95% CI = 1.06–1.26, p = 0.001), with a risk significant in patients with coronary stents (HR = 1.26 95% CI = (1.16–1.38) p < 0.00001), and an increased risk of stent thrombosis (HR = 1.21 95% CI =1.03–1.42 p = 0.02) (Luo et al., 2023).

We present the case of a woman who had concomitant gastrointestinal bleeding due to a Dieulafoy lesion and an acute myocardial infarction. She was managed with high doses of omeprazole and taken to stent implantation and initiation of DAPT with ASA and clopidogrel. Subsequently, she presented recurrent thrombosis of the stent with a fatal clinical outcome as an example of the possible clinically relevant drug interactions between omeprazole and clopidogrel.

CASE DESCRIPTION

A 76-year-old black woman from the Colombian Pacific, with a medical history of arterial hypertension, poorly controlled type 2 diabetes mellitus, and active smoking of 12 packs/year. One week prior to admission and on the day of admission, she presented episodes of emesis in a coffee cup.

He consulted the emergency department due to typical angina of 4 hours of evolution. On admission, her vital signs were heart rate: 90 bpm, respiratory rate: 14 rpm, blood pressure: 161/72 mm Hg, temperature: 36.2°C, oxygen saturation: 96% at ambient, blood glucose: 208 mg/dl. Her weight was 90 kg, height 1.70 m and BMI 31 kg/m2. She presented mucocutaneous pallor, no jugular venous distention, cardiopulmonary auscultation was normal, and no lower limb edema.

A 12-lead electrocardiogram was performed that showed sinus tachycardia, ST depression in the lateral and inferior wall, and T inversion in the lateral wall (Figure 1). The blood count on admission showed a hemoglobin of 6.5 g/dL. The initial troponin was negative (0.070 ng/ml, ULN: 0.34 ng/ml) with a second troponin that was positive at 3 hours (0.546 ng/ml, ULN: 0.34 ng/ml). Dual antiplatelet therapy was not started due to the recent history of gastrointestinal bleeding and severe anemia.

Ten hours after admission, the patient presented a new episode of coffee bean emesis and general weakness. Omeprazole was started immediately as a continuous infusion at 8 mg/hour for 72 hours and subsequently 40 mg IV every 12 hours. She required a transfusion of two units of red blood cells.

Six hours after the episode of gastrointestinal bleeding, the patient underwent upper gastrointestinal endoscopy, finding a Deaulafoy lesion with layer bleeding that required sclerotherapy.

After five days of endoscopic management, the patient underwent diagnostic coronary angiography where a severe compromise of the anterior descending artery was found, which was intervened with angioplasty and medicated stent implantation and subsequently ASA 100 mg/day and clopidogrel 75 mg/day were started.

Twelve hours after the coronary intervention, the patient presented a new episode of severe angina and the electrocardiogram showed diffuse ST elevation in the anterolateral wall (Figure 2). She was immediately taken to catheterization where acute stent thrombosis was found in the middle segment of the left anterior descending artery. She underwent

thromboaspiration and in-stent medicated stent angioplasty.

Eighteen hours after the second procedure, the patient presented again with angina and cardiogenic shock requiring dobutamine and norepinephrine. The electrocardiogram showed widening of the QRS with diffuse ST elevation in the precordial leads and elevation in aVR (Figure 3). She was rushed to coronary angiography where the left anterior descending artery was found to be occluded from its origin. She underwent intracoronary thrombolysis with alteplase without success. Due to clinical instability, it was considered that the patient did not benefit from surgical management. Six hours later, the patient presented cardiorespiratory arrest with pulseless electrical activity rhythm. After 21 minutes of advanced cardiopulmonary resuscitation, return to spontaneous circulation was not achieved and death was declared.

DISCUSSION

The drug interaction between clopidogrel and omeprazole has been exposed in pharmacological studies, where it has been shown that omeprazole has an irreversible or quasi-irreversible inhibitory effect on the CYP2C9 enzyme. Omeprazole, even at low doses, generates a significant increase in the area under the curve (AUC) of the substrates of other drugs, which decreases the availability of their active metabolites (Ogilvie et al., 2011), which could favor the outcomes. adverse events presented in our patient, who required high doses of this drug for a long time due to her episode of digestive bleeding. However, the clinical relevance of this interaction is still controversial with conflicting results in observational studies, clinical trials and meta-analyses (Bhatt et al., 2010; Bundhun et al., 2017; Cuisset et al., 2009; Drepper et al., 2009). al., 2012; Khan et al., 2019; Luo et al., 2023; O'Donoghue et al., 2009; Tentzeris et al., 2010).

These associations have led entities such as the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to recommend against the concomitant use of omeprazole and clopidogrel (Guerin et al., 2016; Sharma et al. al., 2010). Currently, the debate on this drug interaction persists, and the validity of these recommendations continues to be questioned (Guerin et al., 2016).

In the case of our patient, it is also important to take into account that both uncontrolled hypertension, uncontrolled diabetes, active smoking, and severe anemia are predictors of thrombotic events that could have contributed to the clinical outcome. There is a relationship between the anemia produced by bleeding and the increased risk of arterial thrombosis, explained by the increase in platelet aggregation and the decrease in fibrinolytic activity as a mechanism to control bleeding (Kim & Kang, 2000).

This case is intended to reawaken concern about drug interactions between clopidogrel and omeprazole, which may be influenced by the dose and timing of PPI administration as well as other individual factors that may increase the risk of thrombosis. Studies to date are inconclusive and decisions about the choice of drug therapy must be made on an individual basis.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest at the time of publication.

FINANCING SOURCE

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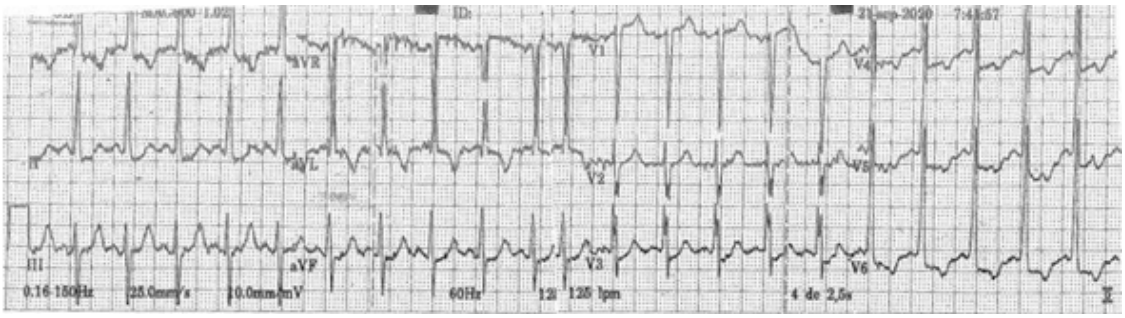

Figure 1. Entrance surface electrocardiogram. Sinus tachycardia is seen at 125 beats per minute, axis at 0°, ST segment depression in V3-V6, DI, DII, aVL and aVF, with ST elevation in aVR and T wave inversion in V4-V6, DI and aVL.

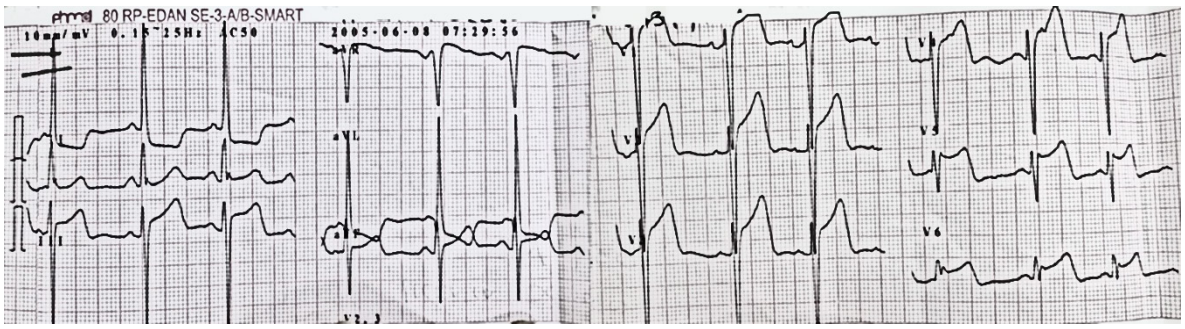

Figure 2. Surface electrocardiogram when presenting with angina after the initial cardiac catheterization. Sinus rhythm is seen with axis at 0°, significant ST segment elevation in V1-V6, DIII, aVF and aVR, with a decrease in DI and aVL.

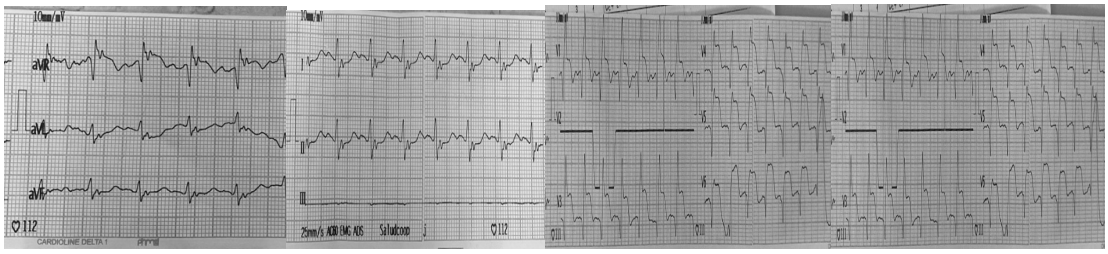

Figure 3: Surface electrocardiogram during cardiogenic shock. Widening of the QRS with diffuse ST elevation in the precordial leads and elevation in aVR can be seen.

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