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Case Report: Aspirin and Ibuprofen – a Potential Life-threatening Drug Interaction after Coronary Stent Implantation

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Summary

A 79-year old man with previous percutaneous coronary intervention in 2007 and a history of stent thrombosis in 2008 and in 2011 was transferred to our department with cardiogenic shock due to acute ST-elevation myocardial infarction. Acute coronary angiography showed thrombotic stent occlusion in both, the left anterior descending coronary artery (LAD) and in the right coronary artery (RCA). Both occlusions were reopened successfully, and the patient could leave the Intensive Care Unit several days later.

The patient's history revealed that he has been treated for spondylodiscitis with antibiotics and ibuprofen for several days. Ticagrelor had been stopped for several days, but aspirin was continued. Surprisingly, the initial platelet function test on admission in our hospital showed no antiplatelet effect of aspirin. We suspected an interaction between aspirin and ibuprofen and stopped ibuprofen treatment. Several days later the platelet function test demonstrated an excellent effect of aspirin.

This report illustrates, that the potential pharmacodynamic interaction between aspirin and non-steroidal anti-rheumatics (NSAR) may result in clinically meaningful life-threatening events.

Case Report

A 79-year old man was transferred to our department with acute myocardial infarction. He presented with severe chest pain and was in cardiogenic shock. Echocardiography showed a severely reduced left ventricular function. The patient had a longstanding history of coronary artery disease and had received a drug-eluting stent (Cypher) in the LAD and three drug-eluting stents (Endeavor) in the RCA in 2007. In the following year the patient experienced an acute anterior myocardial infarction due to stent-thrombosis of the LAD. The patient received another 3 drug-eluting stents (DES) (Taxus) in the LAD and 2 DES (Promus) in the RCA. In 2011 he was again admitted with ST-elevation myocardial infarction. Acute coronary angiography showed again a thrombotic stent occlusion of the LAD. The vessel was reopened and another DES (Xience) was implanted. Since this time the patient was on long-term antiplatelet therapy with aspirin and ticagrelor.

On October 1, 2012, he was admitted to our associated hospital because of neck pain and was diagnosed to have spondylodiscitis. Analgetic and antibiotic treatment was initiated.

The onset of chest pain was on October 11, 2012 at approximately 6:00 a.m. An electrocardiogram was performed at this time and showed acute myocardial infarction (Fig. 1).

Immediate coronary angiography revealed thrombotic occlusion of both, the proximal LAD and the proximal RCA (Fig. 2 a, b) requiring implantation of a DES (Xience) in the LAD and a balloon dilatation of the RCA. In order to stabilize the patient an intra-aortic balloon pump was implanted and the patient was transferred to the Intensive Care Unit. Aspirin and ticagrelor as well as continuous intravenous low molecular heparin were administered.

Since the patient had suffered his 3rd stent thrombosis, a platelet function test was performed. The effect of aspirin was measured using the PFA 100 test. Collagen/Epinephrine closure time of only 84 sec. was found, which indicated an insufficient antiplatelet effect of aspirin. In order to assess the effect of ticagrelor, the Platelet VASP/P2Y12 test was performed and showed a moderate effect of ticagrelor (Platelet Reactivity Index of 52%).

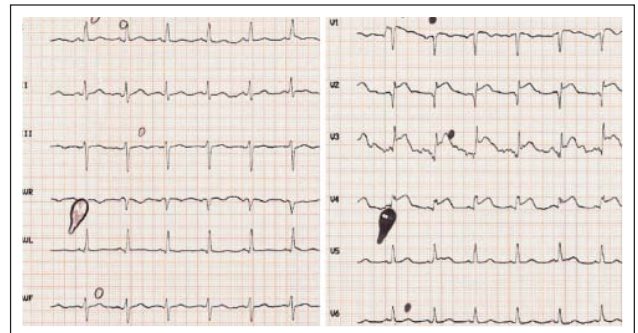


Figure 1: Initial ECG showing ST segment elevations in lead V₁–V₄.

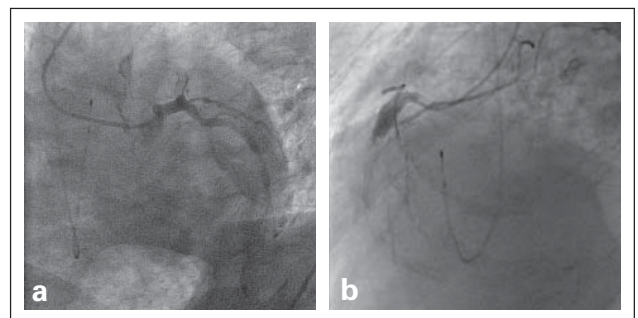


Figure 2: (a): Coronary angiography showing stent thrombosis of the left descending coronary artery (LAD); (b): Coronary angiography showing stent thrombosis of the right coronary artery (RAC).

A further detailed history was undertaken with the treating physician of the referring hospital, which revealed that therapy with ticagrelor had been discontinued 6 days before and that the patient had continuously received ibuprofen 400 mg twice daily for pain relief during the last 10 days.

Accordingly, an interaction between aspirin and ibuprofen, causing the reduced antiplatelet effect of aspirin, was suspected. We therefore stopped therapy with ibuprofen and switched to paracetamol. Another platelet function test 4 days later indeed documented an excellent effect of aspirin with a PFA 100 closure time of over 300 sec., and an excellent effect of ticagrelor with a Platelet Reactivity Index of 9%.

After removing the intra-aortic balloon pump 4 days later, the patient was extubated and was discharged after 35 days in good clinical condition under permanent dual antiplatelet-therapy with aspirin and ticagrelor.

■ Discussion

Stent thrombosis is a serious complication after stent implantation. Up to 60% of all cases with stent thrombosis occur within the first 30 days after percutaneous coronary intervention (acute and subacute stent thrombosis) [1], while the other 40% of cases occur late (up to 1 year) or very late after stent implantation. According to the Swedish Coronary and Angioplasty Registry the cumulative incidence of stent thrombosis at 1 year was 1.1% with bare-metal stents (BMS) compared to 0.4–0.8% with DES [2].

Numerous risk factors for the development of stent thrombosis have been identified, which can be classified as procedural or lesion-related, patient-related or stent-related [3]. In addition, genetic factors may play a role in the response to antiplatelet-drugs (eg, clopidogrel-non-responder) [4], and interruption or cessation of antiplatelet therapy is a main risk-factor for stent thrombosis [3].

The history of our patient was remarkable and included already 2 events of stent-thrombosis in the past. Furthermore, presence of multiple and overlapping stents have to be discussed as an additional risk-factor for stent-thrombosis in our patient [5]. The patient-related risk-factors were renal failure, advanced age and a low ejection-fraction [3, 5]. Because of this history of stent-thrombosis the patient had already received prolonged dual antiplatelet-therapy (DAPT) since 2011.

The most recent event of stent-thrombosis in both vessels occurred under particular circumstances:

1. Our patient suffered from acute spondylodiscitis. Acute inflammation increases platelet-function and can also lead to activation of the coagulation-system [6].
2. Ticagrelor, a potent reversible ADP-receptor platelet antagonist, had been withdrawn 6 days before the acute event. Interruption was considered necessary to enable surgical treatment of spondylodiscitis.

According to recent guidelines, the ADP-receptor antagonist is usually stopped 1 year after DES implantation, while aspirin is continued lifelong. However, prolonged DAPT after 1 year may be useful in patients with a higher risk for

stent-thrombosis. A history of stent-thrombosis is considered as strong risk-factor for a future stent-thrombosis and therefore lifelong DAPT was probably indicated in the present patient [3].

3. The result of the platelet function test showed an insufficient effect of aspirin, although this medication had been taken without any interruption. For this reason a pharmacodynamic interaction between ibuprofen and aspirin has to be suspected.

Aspirin irreversibly acetylates and inactivates the enzyme cyclooxygenase-1 (COX-1), which leads to the inhibition of platelet-aggregation. The binding site for aspirin and for ibuprofen lies within a narrow hydrophobic channel within the core of the enzyme cyclooxygenase [7]. The presence of ibuprofen interferes with aspirin binding and the mechanism of this interaction is steric hindrance at the active site of COX-1, preventing irreversible platelet-aggregation [8, 9]. It has been shown, that the antiplatelet-effect of aspirin is reduced if ibuprofen is added within the last 2 hours before aspirin-intake. Conversely, the antiplatelet-effect of aspirin is not influenced, if ibuprofen is administered 2 hours after aspirin-intake [10]. In our case ibuprofen was prescribed in the morning and evening, and aspirin was taken at noon.

Studies also have shown that other NSAIDs like indomethacin, mefenamic acid, tiaprofenic acid and naproxen may influence the antiplatelet-effect of aspirin while diclofenac, paracetamol and celecoxib seem to be safe when added to aspirin [7–9]. Nevertheless, cardiologists as well as caring physicians should be aware of this potential interaction of these commonly used drugs and should apply NSAIDs only after careful consideration in patients with a history of stent-implantation.

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