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RIVAROXABAN-INDUCED THROMBOCYTOSIS
A not enough known adverse effect

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INTRODUCTION

Thrombocytosis is a common abnormality in clinical practice. There is no consensus on the exact defintion of thrombocytosis. It includes a very wide range of primitive and secondary etiologies spectrum. There are familial thrombocytosis, clonal thrombocytosis (including essential thrombocytosis due to myeloproliferative disease) and secondary or reactive thrombocytosis [1].
Reactive thrombocytosis are much more common than other causes of thrombocytosis and are associated with underlying conditions such as infection, inflammatory disease, anaemia due to iron deficiency, surgery (especially splenectomy), acute haemorrhage and exposure to certain drugs [1,2]. Some authors reported cases of thrombocytosis with low molecular weight heparin (LMWH) [2-6]. In june 2000, a french Pharmacovigilance study has found 51 notifications of thrombocytosis (> 500 000 platelets/mm^3) associated with LMWH in the French Pharmacovigilance Database. In all cases, patients were asymptomatic and thrombocytosis was accidentally discovered. On average, patients had completed 12 days of treatment at the time of discovery of thrombocytosis. This side effect disappeared without complication in 41 cases, the outcome is unknown for the 10 other cases [7]. The pathophysiologic mechanism is not fully understood but it is established that heparin stimulates megakaryocytopoiesis. The mechanism of action involves a neutralization of inhibitory of platelet factor 4 (PF4) and transforming growth factor (TGF-β) on megakaryocyte proliferation. There is also a synergistic action with many growth factors such as interleukin 6 (IL6), GM-CSF, erythropoietin, stem cell factor but not with interleukin 3 (IL3). Finally, a potentiating action of thrombopoietin factor favouring predominantly megakaryocytopoiesis was also highlighted [2]. This risk reinforces the importance of regular monitoring of platelets during heparin therapy.
In secondary thrombocytosis, platelets are qualitatively and functionnaly normal. Complications (such as thrombotic or haemorrhagic events) do not occur normally and thrombo-haemorrhagic risk, if it existed, would be related to the underlying disease and not to thrombocytosis. The occurrence of these risks in a patient with secondary thrombocytosis must lead to a clonal component associated search. The treatment of reactive thrombocytosis is the treatment of the causal disease [1]. Whatever the cause of thrombocytosis, his supervision should never be neglected because the combination of several etiologies is possible and could increase the thrombocytosis. To our knowledge, there is no case report of thrombocytosis with oral direct anticoagulants in the literature. We report a case of a woman treated with rivaroxaban who developed thrombocytosis.

OBSERVATION

- This case concerns a 77-year-old female patient with a medical history of allergy to penicillin, breast cancer, hiatus hernia, gastroesophageal reflux disease, high blood pressure, dyslipidaemia and pulmonary tuberculosis.
- The patient is currently treated by aspirin, pantoprazole, fenofibrate, cicletanine and bromazepam.
- On the 3rd of march 2014, the patient started a treatment with rivaroxaban (10 mg per day) to prevent venous thromboembolism after an orthopaedic surgery.
- On the 17th of march, thrombocytosis is fortuitously highlighted on a complete blood count, with a rate of 1024000/mm^3 platelets (figure 1).
- There was no other bloodlines abnormality and no inflammatory syndrome was found. Deep or superficial thrombosis was not present.
- The treatment with rivaroxaban was discontinued and substituted for LMWH.
- The outcome was favourable with a rate of 288000/mm^3, 15 days after the stop of the drug.

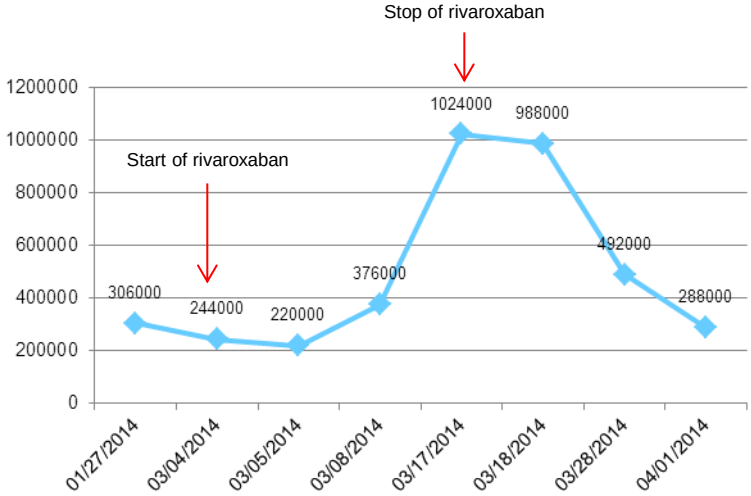

Figure 1: Rate of platelets (normal values: 150000 - 400000/mm^3)

DISCUSSION - CONCLUSION

Thombocythemia is an uncommon side effect observed in prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. This side effect is reported in the Summary of Products Characteristics (SPC) of rivaroxaban in Europe [8], but not in reference books such as Martindale® or in the Drugdex ® database [9]. To our knowledge, there are no cases reported in the literature with rivaroxaban. However, some cases were notified in the French Pharmacovigilance Database (including one case with positive rechallenge, as well as some cases describing a thrombocytosis with more than 1000000 platelets/mm^3). In these cases, the discovery of reactive thrombosis is generally fortuitous because this effect is asymptomatic. Most often, the outcome is favourable after discontinuation treatment. Some cases are also reported in the Pharmacovigilance Database of the World Health Organisation (Vigilyze®).
Rivaroxaban is a factor Xa inhibitor and these cases may look like the cases of thrombocytosis observed with heparins. However, it is unclear if the cases of thrombocytosis associated with rivaroxaban can be explained in the same way as for LMWH because the two drugs have different sites of action: rivaroxaban directly inhibits factor Xa, whereas LMWH exert their anti-Xa activity by activating antithrombin III.
Apixaban is another new factor Xa inhibitor, but this adverse effect is not mentioned in the SPC, in the Martindale® or in the Drugdex® database. To date, no case of thrombocytosis is reported in the literature, in the French Pharmacovigilance Database or in Vigilyze® with apixaban.
Some cases of thrombocytosis are notified with dabigatran, factor IIa inhibitor, in the French Pharmacovigilance Database and in Vigilyze® but this side effect is not mentioned in the SPC or in the reference books and we did not find any case in the literature.

The physicians should keep in mind this possible adverse effect of thrombocytosis induced by rivaroxaban and the decrease with withdrawal. The thrombotic risk, even low, should not be overlooked.

References:

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