Spontaneous Splenic Rupture of a Patient Treated with Rivaroxaban

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Introduction

Rivaroxaban is a novel anticoagulant and a direct factor Xa inhibitor that targets the prothrombin-binding site responsible for the conversion of prothrombin to thrombin. It is commonly used to lower the risk of stroke and systemic embolism in non-valvular atrial fibrillation and for the treatment of deep vein thrombosis and pulmonary embolism [1]. In addition, it has recently been approved by the US Food and Drug Administration (FDA) after the COMPASS trial, which showed a 24% risk reduction of major cardiovascular events in patients with chronic coronary artery disease and peripheral artery disease [2]. The most common adverse effect of Rivaroxaban is related to the increased risk of bleeding. We are reporting the sixth case of spontaneous splenic rupture caused by Rivaroxaban. Written permission to publish this case was obtained from the patient.

Case Presentation

A 66-year-old gentleman with a background of hypertension and chronic atrial fibrillation, treated with Enalapril 20 mg (two times daily), Bisoprolol 5 mg (once a day) and Rivaroxaban 20 mg (once a day), was admitted to the Emergency Department with abdominal pain, nausea, and vomiting. He was a smoker but denied any alcohol intake.

On examination, he was tachycardic (115 bpm), hypotensive (BP 70/50 mmHg), had abdominal distention with tenderness in the epigastrium and left hypochondrium. Fluid resuscitation was commenced with crystalloids, and a Noradrenaline infusion was started via a PICC line (Peripherally Inserted Central Venous Catheter). Initial blood tests revealed Hemoglobin (Hb) of 11 g/dL with a normal platelet count (150.000/μL), and a coagulopathy [Prothrombin Time (PT) 43%, INR 1.93, activated Partial Thromboplastin Time (aPTT) 50 sec and fibrinogen 1.43 g/dL]. Arterial blood gas sampling confirmed metabolic acidosis (pH 7.22, PO₂ 93 mmHg and PCO₂ 35 mmHg) and a Computed Tomography (CT) of the abdomen/pelvis with intravenous contrast was undertaken, revealing a splenic rupture with a moderate hemoperitoneum (Figure 1A,1B). The patient reaffirmed there was no trauma prior to the onset of abdominal pain. A repeat full blood count was performed and confirmed a significant decrease in Hb(5.7 g/dL) and hematocrit (17.6%). Two units of Red Blood Cells (RBC) were transfused immediately, and the patient transferred to the operating room for emergency laparotomy and splenectomy.

An arterial line inserted prior to induction revealed severe hypotension (50/20 mmHg) requiring administration of small boluses of intravenous Adrenaline (5 μg + 5 μg). General anesthesia was initiated with a rapid sequence induction (Etomidate 18 mg, Fentanyl 150 μg, Rocuronium 80 mg). Intubation was uneventful, and anesthesia was maintained with Sevoflurane and Remifentanil. A percutaneous sheath introducer with a 8.5 French was inserted under US guidance into the right internal jugular vein to facilitate rapid administration of blood products. Four units of RBC and three units of Fresh Frozen Plasma (FFP) in addition to 500 mL of colloids and 500 mL of crystalloids were required during surgery aiming to stabilize the patient and reverse the coagulopathy. A total splenectomy was performed, and after safe extubation in the operating room, was transferred to the intensive care unit. His postoperative course was uneventful and successfully discharged home seven days later.

Discussion

Rivaroxaban has a rapid onset of action with a relatively predictable pharmacokinetic profile and a relatively short plasma half-life making initiation, maintenance, and discontinuation of anticoagulant therapy considerably more comfortable than with traditional oral anticoagulants. It is highly protein-bound (92% to 95%) with renal excretion at 36%, and in contrast to other new anticoagulants as Dabigatran, dialysis is not effective for its removal.
Table 1: Management of bleeding secondary to Rivaroxaban.

<table>
<thead>
<tr>
<th>Rivaroxaban</th>
<th>Moderate bleeding: action</th>
<th>Severe bleeding: action</th>
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<tbody>
<tr>
<td></td>
<td>• Fluid replacement.</td>
<td>• Add recombinant factor VIIa (Novoseven® 100 μg/kg by IV bolus); repeat if necessary*3</td>
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<tr>
<td></td>
<td>• Give blood cells if Hb&lt;8 mg/dL if patient is taking an antiplatelet drug</td>
<td>• Give Andexanet alfa if available*4</td>
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<tr>
<td></td>
<td>• Give platelets (if &lt;75,000/μL)</td>
<td>• Bolus 800 mg at 30 mg/minute.</td>
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<td></td>
<td>• Tranexamic acid iv (15-30 mg/kg) +/- continuous infusion (1 mg/kg/h)</td>
<td>• Within 2 minutes following the bolus dose, administer the continuous iv infusion 8 mg/min for up to 120 minutes.</td>
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<td></td>
<td>• Consider Prothrombin complex 50 IU/kg, repeat if necessary*5</td>
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*1 There is limited data available on the effectiveness of prothrombin complex in patients taking Rivaroxaban.
*2 The effect of recombinant factor VIIa in patients taking Rivaroxaban is currently uncertain.
*3 Half dose could be an option if there is no a life-threatening bleeding scenario.

In 2019 the update of the AHA/ACC/HRS in the guidelines for the management of patients with atrial fibrillation, Rivaroxaban is now recommended over warfarin for stroke prevention [3]. There is, at present, no consensus on the best methodology for assessing Rivaroxaban activity in vivo and hence no guiding dosage. Unlike traditional oral anticoagulants, traditional coagulation tests cannot be used to assess or adjust dosing. At therapeutic concentrations, Rivaroxaban has a relatively weak influence on the PT; however, it is more profound at higher concentrations, with a good correlation between prolongation of the PT and plasma concentration.

Although hemorrhage is the significant adverse effect of Rivaroxaban, unfortunately, there is no immediate reversal agent currently available. Although Andexanet alfa has been approved by the FDA, for reversal of anticoagulation in life-threatening or uncontrolled bleeding in patients treated with Rivaroxaban, it is not available in many countries. Therefore, other measures should be taken to treat significant hemorrhage (Table 1).

Conclusion

Rivaroxaban’s datasheet details no reference to spontaneous splenic rupture due to its use; however, this is the sixth case report of spontaneous splenic rupture in a patient, with no history of trauma, treated with Rivaroxaban.

A pharmacologic interaction could be the potential cause of an increase in activity of Rivaroxaban resulting in major hemorrhage. An interaction between amlodipine and telmisartan/hydrochlorothiazide was reported as a cause of hemorrhage in a previous case report [4]. An interaction between amiodarone, a P-glycoprotein inhibitor and Rivaroxaban has also been reported as a cause of spontaneous splenic rupture [5].

It’s well known that the higher risk of bleeding exists when Rivaroxaban is used in combination with antiplatelet agents, particularly in the elderly or in the presence of renal dysfunction. Specifically, of the case reports described previously one had aspirin as a potential cause and another reported renal dysfunction as the potential cause [6]. Similar to the case we are reporting, another could not ascertain a potential cause [7]. We believe there are significant numbers for the pharmaceutical manufacturer to mention splenic rupture in the datasheet and doctors need to be made more aware of this severe complication of patients prescribed Rivaroxaban [8].

References