CASE REPORT

The Successful Prevention of Thromboembolism Using Rivaroxaban in a Patient with Antithrombin Deficiency during the Perioperative Period

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Abstract:
Antithrombin (AT) deficiency, a rare disorder of the coagulation system, is a serious risk factor for thromboembolism. Approximately 50-90% of patients with AT deficiency develop thromboembolism during their lifetime. In addition, surgery is a major risk factor for thromboembolism in these patients. We herein report the case of a 90-year-old woman with AT deficiency who was safely and successfully managed using rivaroxaban (a direct oral factor Xa inhibitor) during the perioperative period of surgery for right femur fracture. The present case illustrates the effectiveness of rivaroxaban in preventing thromboembolisms due to surgery, even in very elderly patients with antithrombin deficiency. Further investigations are needed to determine the optimal dosage of rivaroxaban.

Key words: antithrombin deficiency, perioperative period, rivaroxaban, elderly patients

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Introduction

Antithrombin (AT) is a glycoprotein composed of 432 amino acids with a molecular weight of 65,000. It is mainly synthesized in the liver and functions as an anticoagulant factor, inhibiting serine proteases, including thrombin and activated coagulation factors IX, X, XI, and XII. AT can bind to unfractionated heparin, which enhances the AT activity. However, a low AT activity causes a hypercoagulable state, and patients with <60% AT activity are reported to be at a high risk for thromboembolism (1).

AT deficiency, identified as the first inherited thrombophilia in 1965, is a rare autosomal dominant disorder of the coagulation system and occurs in approximately 0.02-0.25% of the overall population (2). Its diagnosis is based on the AT antigen level, AT activity and a family history of AT deficiency. Type 1 disease is AT deficiency, which is characterized by reduced AT activity due to a low antigen level, while Type 2 disease shows a functional defect of the AT activity.

AT deficiency is a major risk factor for thromboembolism. Approximately 50-90% of patients with AT deficiency develop thromboembolism during their lifetime (3). Furthermore, approximately 60% of patients with AT deficiency experience their first thromboembolism by 15-35 years of age (4). These thromboembolisms are characterized by their frequent and repeated intravenous occurrence in patients with a family history of AT deficiency. They are easily generated by various triggers, including surgery, trauma, long airplane flights, pregnancy, delivery, infection and exposure to estrogen (5). When patients with AT deficiency are exposed to these risks, preventive therapy, including the administration of oral anticoagulants and intravenous AT, should be considered (6). In addition, patients with a history of thromboembolism need to take oral anticoagulants on an ongoing basis.

Rivaroxaban, a direct oral factor Xa inhibitor, is effective...
for the treatment and prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE). Rivaroxaban has been shown to be non-inferior to existing treatments (such as warfarin or low-molecular-weight heparin) for preventing the recurrence of symptomatic DVT and PE (7). The frequency of adverse effects, such as serious hemorrhaging, in patients receiving rivaroxaban is comparable to that in patients receiving existing treatments. Thus, the safety and efficacy of rivaroxaban have been ensured.

We herein report the case of 90-year-old woman with AT deficiency who experienced no thromboembolic events after the administration of rivaroxaban as a preventive treatment during the perioperative period. This is first report of the use of rivaroxaban in the treatment of a very elderly patient with AT deficiency.

**Case Report**

A 90-year-old woman was diagnosed with AT deficiency at 82 years of age. Her elder daughter was first diagnosed with AT deficiency due to PE after a long airplane flight. At that time, several members of her family were examined, and the patient, her younger daughter and a female grandchild were found to have AT deficiency as well. Details regarding the patient’s data at the time of the diagnosis and the type of AT deficiency were unknown. She had no history of thrombosis, including DVT or PE; however, she had been prophylactically treated with warfarin since the diagnosis.

The patient was diagnosed with a fracture of the right femur due to a fall. Open reduction and internal fixation was planned. Five days prior to the surgery, the laboratory data showed the following: albumin, 4.0 g/dL (normal range: 4.0-5.0 g/dL); aspartate aminotransferase (AST), 21 IU/L (normal range: 7-38 IU/L); alanine aminotransferase (ALT), 15 IU/L (normal range: 4-43 IU/L); total cholesterol, 174 mg/dL (normal range: 120-220 mg/dL); AT activity, 34% (normal range: 70-130%); prothrombin time (PT), 13.7 sec (normal range: 10-14 sec); activated partial thromboplastin time (APTT), 31.5 sec (normal range: 25-36 sec); fibrin degradation product (FDP), 23 μg/mL (normal range: <5.0 μg/mL); D-dimer, 10 μg/mL (normal range: <1.0 μg/mL); protein C activity, 70% (normal range: 64-146%) and protein S antigen level, 75% (normal range: 65-135%). Pre-operative computed tomography (CT) showed that the left distal popliteal vein was poorly depicted, suggesting venous occlusion due to micro DVT. The elevation of the patient’s FDP and D-dimer levels also supported the existence of micro DVT due to her gait disturbance.

Two days before surgery, warfarin was switched to heparin, which was administered intravenously until 6 hours before surgery. Heparin was administered at a dose of 18 U/kg/h; her body weight was 40 kg, so approximately 17,000 U/day was administered. At the same time, concentrated AT (37.5 U/kg; 1,500 U/day) was administered for 6 days. On the day of surgery, the patient’s AT activity increased to 76% and reached a normal level. The surgery was finished safely without intraoperative bleeding.

On postoperative day 1, treatment with oral rivaroxaban was initiated in place of heparin to prevent DVT. The laboratory data on postoperative day 14 showed the following: AT activity, 41%; PT, 13.5 sec; APTT, 29.3 sec; FDP, 9 μg/
mL and D-dimer, 4 μg/mL (Figure). The levels of FDP and D-dimer, which had been elevated before surgery and on the day of the surgery, were normalized. The patient took rivaroxaban continuously while undergoing rehabilitation to improve her walking function. No thromboembolic events occurred for at least three months.

Discussion

Thrombophilia in patients with AT deficiency is a serious problem. In addition, although AT deficiency is a major risk factor of thromboembolism, the surgical treatment of serious complications in these patients is often unavoidable. In the present case, a 90-year-old woman with AT deficiency was successfully and safely managed using rivaroxaban to prevent thromboembolism during the perioperative period. While a few reports have described the use of rivaroxaban to treat AT deficiency (8-10), none have reported the outcome in a very elderly patient, such as in the present case.

Continuous heparin infusion and the oral administration of warfarin have been previously used as the standard anticoagulant therapy to prevent thromboembolisms during the perioperative period in patients receiving anticoagulants. The reduction in the AT activity that occurs following the administration of heparin means that the AT activity must be improved before the administration of heparin. In addition to appropriate supplementation with concentrated AT, the dose of warfarin is controlled from 1.5 to 2.5 based on the international normalized ratio of prothrombin time. Bleeding tendency is often a serious problem during the perioperative period; as such, patients’ anticoagulant status should be closely monitored. These types of management are further complicated, especially in patients with thrombophilia (including AT deficiency) (11).

Direct oral anticoagulants (including rivaroxaban) are now being used instead of warfarin to prevent thromboembolism. Rivaroxaban has a number of advantages over warfarin, such as its rapid pharmacological efficacy. In addition, there is no need for anticoagulant monitoring, and rivaroxaban is not influenced by diet, nor does it interact with other agents (12). For these reasons, rivaroxaban is recommended in many patients, including elderly individuals. Rivaroxaban is administered once a day as maintenance therapy. Its bioavailability is higher than other direct oral anticoagulants.

In addition, rivaroxaban is the only medicine that has been proven to be safe and effective for Japanese patients with symptomatic DVT or PE (13). The administration of rivaroxaban does not usually require a dose adjustment. However, care must be taken to avoid overdose, which may result in hemorrhagic events, especially in patients who are older than 75 years of age, those who have renal dysfunction and those with low body weight. The present case involved an elderly patient with a low body weight and a low creatinine clearance (Ccr 35 mL/min). We decided that the dose of rivaroxaban should be decreased to 10 mg/day. This resulted in a favorable course without thrombotic or hemorrhagic events before or after the operation.

It has been reported that maintaining an AT activity of >80% is effective in preventing thromboembolic events during the perioperative period (14); however, there is currently no evidence regarding the benefits of using concentrated AT. Although patients with a history of thromboembolisms are recommended to take oral anticoagulants throughout their lifetime, patients with no history of thromboembolisms should be prescribed oral anticoagulants only when they are exposed to risk factors (this includes the perioperative period). The continuous use of oral anticoagulants is not recommended because it is associated with an increased risk of bleeding (15). The present case involved an elderly patient who would be immobile for a long time due to leg surgery. She therefore received long-term oral anticoagulant treatment. Although the optimal period for anticoagulant treatment remains to be determined, it should be continued until the patient is able to walk stably.

In conclusion, rivaroxaban proved to be effective in preventing thromboembolism during the perioperative period in an elderly patient with AT deficiency. However, no evidence has yet been obtained regarding the optimal dosage to prevent thromboembolic events in at-risk patients with AT deficiency, especially during the perioperative period. Further studies in a greater number of cases will help clarify the optimum rivaroxaban administration regimen in these rare situations.

The authors state that they have no Conflict of Interest (COI).

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