

In Three Cases, the Use of Dabigatran was Found to be Associated with Factor VIII Inhibitors and Prolonged APTT

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Abstract

We report the use of dabigatran was found to be associated with Factor VIII inhibitors and prolonged APTT in the three cases. Taking the dabigatran was recognized prolonged APTT, low titer Factor VIII inhibitors and reduction of Factor VIII. Once these cases stopped dabigatran in a variety of causes. At the time of dabigatran discontinuation, APTT was normal value and Factor VIII, Factor VIII inhibitor became the normal value. When dabigatran resumed, APTT was prolonged and low titer Factor VIII inhibitors and reduction of Factor VIII. Side effects of bleeding at the time of APTT prolongation was not admitted in three cases.

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Introduction

Dabigatran is a novel anticoagulant drug that is thought to work by directly inhibiting thrombin to exert an anticoagulatory effect [1]. In RE-ly trials with comparative tests of dabigatran and warfarin, dabigatran was found to be better at preventing systemic embolism with the same level of risk of hemorrhagic complications [2]. Unlike warfarin, dabigatran has the advantage of requiring no coagulation monitoring. However, it has been reported that many hemorrhagic complications have been caused by dabigatran in cases with prolonged activated partial thromboplastin times (APTT) [3-7]. Although the reason for this is unclear. We recently reported on three cases where a reduction of factor VIII and the presence of a low titer of factor VIII inhibitors were observed in blood tests performed during prolonged APTT in patients taking dabigatran [8].

Materials and Methods: Coagulation and inhibitor assay

Blood samples were collected in a trough in the morning

before administration of dabigatran. PT and APTT were measured using SynthASil. We measured the activities of factor VIII, using HemosIL coagulation factors. These results were analyzed by ACL TOP (Instrumentation Laboratory, Tokyo, Japan). Factor VIII inhibitor assays were conducted using serial dilution of patient plasma incubated with equal volumes of normal plasma for 2h at 37°C. The residual factor VIII levels of the incubation mixtures were measured. Positive results indicated a significant decrease in the residual factor VIII was plotted against each other, and the inhibitor titers were obtained by linear regression. By definition, one Nijmegen-Bethesda unit reduces the Factor VIII activity level by 50% [9].

Case 1: Female, 68 years old

Patient started on azacitidine in April 2012 due to a diagnosis of myelodysplastic syndrome. During the course of treatment, the patient was found to be suffering from deep vein thrombosis, and was therefore started on dabigatran 110 mg twice daily starting in August 2012. Laboratory data was APTT 30.3 seconds before starting dabigatran. Lupus anticoagulant and antiphospholipid antibodies were negative. A prolonged APTT was subsequently observed so blood tests were performed. A blood test conducted in February 2013 yielded the following results: APTT 50.0 seconds, factor VIII 56%, Factor VIII inhibitor 2BU/ml. No hemorrhagic side effects were observed, but the dabigatran was stopped for one week due to the observation of prolonged APTT. When the dabigatran was stopped, a blood test yielded an APTT of 28.9 seconds, a Factor VIII level of 120%, and no Factor VIII inhibitors. The patient was restarted on dabigatran when elevated D-dimer levels were observed during this stoppage period. A blood test conducted one week after resuming dabigatran yielded an APTT of 51.6 seconds,

a Factor VIII level of 40% and a Factor VIII inhibitor level of 1BU/ml.

Case 2: Female, 69 years old

Receiving chemotherapy for a diffuse large B-cell lymphoma. Past history of nonvalvular atrial fibrillation, which had been treated since March 2013 by starting on dabigatran 110 mg twice daily. Despite observing an APTT of 44.4 seconds, a Factor VIII level of 56% and a Factor VIII inhibitor of 1BU/ml, there were no hemorrhagic symptoms. During this period, the patient developed gallstones that required an Endoscopic Sphincterotomy (EST) operation. It became APTT 40.5 seconds, Factor VIII 120%, Factor VIII inhibitor negative. After operation dabigatran restarted and APTT 46.0 seconds, Factor VIII 56%, Factor VIII inhibitor 1BU/ml one week later.

Case3: Females, 64 years old

Patients started lenalidomide treatment in June 2013 due to a diagnosis of multiple myeloma. She was started on dabigatran 110 mg twice daily after experiencing thrombosis prophylaxis due to the lenalidomide. A blood test conducted before starting dabigatran yielded an APTT 37.5 seconds, a Factor VIII level of 99%, and no Factor VIII inhibitors. After administration of dabigatran for one week, these values became an APTT 57.5 seconds, a Factor VIII level of 38%, and a Factor VIII inhibitor titer of 1 BU/ml. Dabigatran was stopped due to the prolonged APTT and thrombocytopenia due to the lenalidomide. When the dabigatran was stopped, a blood test yielded an APTT 36.3 seconds, a Factor VIII level of 97 %, and no Factor VIII inhibitor. She was again started on dabigatran 110 mg twice daily for thrombosis prophylaxis due to the second course of lenalidomide. A blood test conducted one week after resuming the dabigatran yielded an APTT 55.0 seconds, a Factor VIII level of 52%, and a Factor VIII inhibitor titer of 1 BU/ml, indicating inhibitors.

Discussion

Dabigatran is a novel anticoagulant drug that is thought to work by directly inhibiting thrombin to exert an anticoagulatory effect. Dabigatran affects the activity of many coagulation factors, factor II,V,VIII,IX, as well as the antifactor VIII

inhibitor. Dabigatran emerged factor VIII inhibitor. It does show that the decreased factor VIII activity and increased factor VIII inhibitor activity caused APTT prolongation depending on the dosage and duration of the dabigatran treatment [8].

In the three cases presented here, it was found that inhibitors were detected while dabigatran was being orally administered, but disappeared after stopping the dabigatran, and were detected again when it was resumed. A feature common to these cases is the prolonged APTT observed when inhibitors were detected. Although there have been many previous reports of drug-induced inhibitors [10], almost all of them relate to high-strength inhibitors and none of them mention the detection of inhibitors induced by dabigatran. Since dabigatran is a direct thrombin inhibitor, there should in theory be no prolongation of APTT.

There is report that point out false positives of the factor VIII inhibitor with taking dabigatran [11]. Because of inhibitor development taking dabigatran stop or restart in cases. It is therefore considered that a low-strength factor VIII inhibitor is involved in cases where APTT is prolonged in patients taking dabigatran.

In conclusion, in three cases, the use of dabigatran was found to be associated with factor VIII inhibitors and prolonged APTT. It was found that inhibitors were detected while dabigatran was being orally administered, but disappeared after stopping the dabigatran, and were detected again when it was resumed.

References

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