CASE REPORT

ONLINE EXCLUSIVE

THE PATIENT

71-year-old woman

SIGNS & SYMPTOMS

- Left subconjunctival hemorrhage
- Renal dysfunction
- International normalized ratio of 4.5

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THE CASE

A 71-year-old woman came to our clinic with a left subconjunctival hemorrhage. She had a history of atrial flutter and had received a liver transplant approximately 10 years ago. The patient reported having a procedure 2 weeks before her visit with us to remove a basal cell carcinoma on her lower left eyelid, but had no recent changes in vision or physical damage to the eye.

In the past year, she had been started on dabigatran 150 mg twice daily after developing symptomatic atrial fibrillation. Our patient had also been receiving tacrolimus 3 mg twice daily since her transplant. Other medications she was taking included hydroxychloroquine 200 mg/d for rheumatoid arthritis, propafenone 225 mg twice daily for atrial fibrillation, valsartan 80 mg/d for hypertension, and ranitidine 150 mg/d for reflux.

Venipuncture coagulation tests showed a partial thromboplastin time (PTT) of 75.1 seconds, a prothrombin time (PT) of 46.1 seconds, and an elevated international normalized ratio (INR) of 4.5 (normal range: 0.8-1.2). Point-of-care INR results were not obtained.

A complete blood count (CBC) was unremarkable with the exception of a low platelet count and high red blood cell distribution width (RDW). Our patient's aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were both within normal limits.

Kidney function tests told another story. The patient's serum creatinine (SCr) and blood urea nitrogen (BUN) levels were elevated (1.54 mg/dL and 29 mg/dL, respectively) and her creatinine clearance (CrCl; 30.2 mL/min) suggested moderate to severe renal dysfunction.

The patient's $CHADS_2$ score was calculated as 1, suggesting she had a low-to-moderate risk of stroke.

THE DIAGNOSIS

Our patient had a left subconjunctival hemorrhage and an elevated venipuncture INR. Based on her renal dysfunction, we suspected that her elevated INR was likely due to an excessive dose of dabigatran, as well as an interaction between dabigatran and tacrolimus.

DISCUSSION

Dabigatran is an oral direct thrombin inhibitor approved for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. An important advantage of dabigatran compared to warfarin is that the fixed-dose regimen does not require routine anticoagulation monitoring. In cases where anticoagulation monitoring is needed, PTT is the preferred method.[1]

While PT and INR have generally not been shown to accurately reflect the degree of anticoagulation with dabigatran at therapeutic doses, there have been in vitro reports of elevated INRs with supratherapeutic dabigatran levels.[2,3] At a typical peak therapeutic dabigatran concentration of approximately 184 ng/mL, the INR generally ranged from

1.1 to 1.7.[2] However, at a dabigatran concentration of 1000 ng/mL, the INR was elevated to 4.5,[2,3] which is the same venipuncture INR recorded in our patient. While there have been published reports of falsely elevated point-of-care INR results compared to corresponding venipuncture INR results in patients taking dabigatran,[4,5] a literature review found only a case of an elevated venipuncture INR in an end-stage renal disease patient receiving hemodialysis.[6]

In the case noted above, as well as our patient, an accumulation of dabigatran due to the patient's renal dysfunction likely resulted in high plasma concentrations and therefore an elevated venipuncture INR. The elimination half-life for dabigatran is approximately 14 hours in patients with normal renal function; in a patient with severe renal impairment, the half-life can be up to 28 hours.[7] Our patient's CrCl at the time of presentation was 30.2 mL/min, which indicated moderate to severe renal dysfunction. Based on dabigatran prescribing recommendations, a dose adjustment to 75 mg bid might be appropriate.[1] (Our patient was taking 150 mg bid.)

We do not believe our patient's elevated INR was due to her liver transplant because there were no clinical signs of liver dysfunction. A more likely contributing factor was a drug interaction with tacrolimus. Dabigatran is a moderate affinity P-glycoprotein (P-gp) substrate and tacrolimus is both a P-gp substrate and inhibitor. While an interaction between tacrolimus and dabigatran has not been studied directly, concurrent use of any P-gp inhibitor and dabigatran is contraindicated in patients with severe renal dysfunction (CrCl: 15-30 mL/min).[1] For these theoretical interactions, the Drug Interaction Probability Scale (DIPS) has been developed.[8] In our patient's case, the calculated DIPS score of 5 suggests a probable interaction, likely due to P-gp inhibition. The other medications our patient was taking did not have this interaction and were unlikely to contribute to the elevated INR and subconjunctival hemorrhage.

Our patient was instructed to stop taking dabigatran and return in 3 days for additional lab tests. At her follow-up visit, the lab results were PTT, 34.3 seconds; PT, 11.6 seconds; and venipuncture INR, 1.1. Her CBC was unremarkable and unchanged. Shortly after the follow-up visit, our patient was assessed by her cardiologist. Due to her renal dysfunction, risk of bleeding, and relatively low $CHADS_2$ score, the cardiologist decided to discontinue dabigatran and start her on aspirin.

Concurrent use of any P-gp inhibitor (such as tacrolimus) and dabigatran is contraindicated in patients with severe renal dysfunction.

THE TAKEAWAY

Dabigatran may cause elevated INR levels in patients with renal dysfunction and/or those taking other medications that could interact with dabigatran. Concurrent use of any P-gp inhibitor (such as tacrolimus) and dabigatran is contraindicated in patients with severe renal dysfunction. Despite the lack of required routine laboratory monitoring, renal function and drug interactions associated with dabigatran therapy should be monitored closely. JFP

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