The Patient
71-year-old woman

Signs & Symptoms
- Left subconjunctival hemorrhage
- Renal dysfunction
- International normalized ratio of 4.5

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 CHADS2 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.

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. At a typical peak therapeutic dabigatran concentration of approximately 184 ng/mL, the INR generally ranged from...
Concurrent use of any P-gp inhibitor (such as tacrolimus) and dabigatran is contraindicated in patients with severe renal dysfunction.

References