IMAJ • VOL 14 • JULY 2012

Dabigatran in Recurrent Deep Vein Thrombosis: When One-Size Does Not Fit All

Gilad Twig MD PhD[1,2,3], Ariel Furer MD[1], Gal Yaniv MD PhD[1,4], Leonid Michael MD[2], Rebekah Karplus MD[2] and Howard Amital MD MHA[2,5]

[1]Defense Forces Medical Corps, Israel
[2]Department of Medicine B, [3]Talpiot Medical Leadership Program, and [4]Department of Imaging, Sheba Medical Center, Tel-Hashomer, Israel
[5]Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

KEY WORDS: dabigatran, deep vein thrombosis, pulmonary edema, anticoagulant therapy, warfarin

IMAJ 2012; 14: 454-455

Dabigatran etexilate is an oral thrombin inhibitor that, after conversion to its active form, competitively inhibits the generation of thrombin. In contrast to warfarin, dabigatran is considered less susceptible to dietary and drug interactions or to genetic polymorphisms as its conversion is independent of cytochrome P-450. This theoretically makes laboratory monitoring of dabigatran unnecessary in most situations and thus confers superiority to warfarin, which requires tight monitoring of the international normalized ratio and vitamin K intake. In the current case we describe failure of dagibatran treatment in a patient with recurrent deep vein thrombosis.

PATIENT DESCRIPTION

An 80 year old man with a previous history of three events of DVT was admitted after 2 weeks of increasing difficulty standing on both legs due to pain. The patient had undergone an insertion of an inferior vena cava filter 18 years previously and was currently anticoagulated with the thrombin inhibitor dabigatran (110 mg twice daily). The patient was a retired officer of a parachuting unit. His physical examination revealed mild obesity (body mass index 32 kg/m^2) with mild to moderate bilateral calf tenderness and marked varicose veins. A Doppler ultrasound demonstrated bilateral thrombosis of the ileofemoral veins. The laboratory tests were unremarkable. Dabigatran was discontinued and enoxaparin (1 mg/kg twice daily) was initiated with complete resolution of the calf tenderness and gait difficulty after 2 days of therapy.

Figure A shows the medical history of vein thrombosis and anticoagulant treatment over time. For the past 18 years until 4 months prior to the current admission, the patient was treated with enoxaparin (1 mg/kg twice daily). Ten years before the current admission he was also diagnosed with paroxysmal atrial fibrillation. A Mobitz II atriovenous block was diagnosed 4 months before the current admission and a DDDR pacemaker was implanted; at that point therapy with low molecular weight heparin was changed to dabigatran (110 mg twice a day).

The first and second DVT events were clinically diagnosed a few weeks after he sustained a significant muscular trauma during his parachute training. Between the events symptoms of venous insufficiency developed that included bilateral edema which worsened during the day or after prolonged standing. All tests for hypercoagulable conditions, such as serum concentrations of homocysteine, antithrombin-III, protein S and protein C as well as high titers of antibodies against cardiolipin, β2-glycoprotein and the lupus anticoagulant were normal. Activated protein C resistance (factor V Leiden), prothrombin G20210A mutation and the C677T variant of methylenetetahydrofolate reductase were within normal range. The patient denied a family history of DVT events or recent weight loss.

DVT = deep vein thrombosis

COMMENT

In view of the patient's intensive parachuting career it was assumed that his first event [E1 in Figure A] was probably triggered by repetitive muscular trauma. The latter was shown to increase the risk for DVT within 2–4 weeks after trauma by about eightfold (95% confidence interval 6–20) [1,2]. The development of venous insufficiency is a generated intrinsic risk factor that independently increases the risk for developing DVT by four to fivefold (95% CI 3–6) [2]. These risk factors, together with the patient's history of repetitive DVT events, put him at high risk for developing future DVT events.

In the case presented here, three indications ultimately necessitated life-long anticoagulation: recurrent DVT, the presence of an inferior vena cava filter, and paroxysmal atrial fibrillation (4 points on the CHAD VASC2 scale). The dosage of dabigatran used in this patient was shown to be effective for stroke prevention [3]. Although the higher dose of dabigatran (150 mg twice a day) was shown to be effective for DVT prevention [4], it is not yet formally indicated for recurrent DVT prevention in Israel or the United States [5]. The involvement of both legs was strongly suggestive of an occlusion at the level of the inferior vena cava filter. Data specific for

CI = confidence interval

Thrombotic event	Presumed trigger	Treatment
*E1: DVT (Rt)	Muscular trauma	Muscular trauma
*E2: DVT (Rt)	Muscular trauma	Bed rest
ED: DVT (Rt), PE	Lack of anticoagulation with previous history of DVT	Warfarin for 6 months, IVC filter
E4: DVT (Rt), PE	Sub-therapeutic INR	Life-long warfarin
E5: DVT (bilateral)	Dabigatran failure	Life-long enoxaparin

Schematic illustration of sequence of DVT events and corresponding anticogulant therapy, with the presumed trigger for the DVT event. The first and second DVT events (E1 and E2) were clinically diagnosed, whereas all subsequent events were diagnosed by duplex ultrasound.
IVC = inferior vena cava, DVT = deep vein thrombosis, PE = pulmonary embolism, Rt = right, Bi = bilateral

dabigatran in the subgroup of patients with inferior vena cava filter are lacking.

Regardless of the underlying cause of DVT and the added factor of an inferior vena cava filter in our case, there is evidence that the fixed dose of dabigatran is not ideal for all patients. Connolly et al. [3] showed that dabigatran was not inferior to warfarin but indicated that it was more effective when administered in patients who weighed less than 50 kg or who had a creatinine clearance rate of less than 50 ml/minute. They also showed that the degree of thrombin inhibition is dose-dependent; whereas both tested regimens (110 mg and 150 mg twice daily) were not inferior to warfarin (INR target 2.0–3.0), 150 mg twice a day was superior to warfarin in preventing stroke in patients with atrial fibrillation.

The present case, together with the above data, argue that "one-size" therapy does not necessarily fit all and emphasizes the importance of identifying the subgroup of patients who may require monitoring of their anticoagulation level over time. This would include overweight or obese patients with an intact creatinine clearance, those with a significant history of recurrent DVT under sub-therapeutic INR level, and possibly the presence of an inferior vena cava filter.

INR = international normalized ratio

Corresponding author:
Dr. H. Amital
Head, Dept. of Medicine B, Sheba Medical Center, Tel-Hashomer 52621, Israel
Phone: (972-3) 530-2661
Fax: (972-9) 530-4796
email: hamital@netvision.net.il, howard.amital@sheba.health.gov.il

References

1. Hellmann I, Ellis MH. Prevention of venous thromboembolism in medical patients: recent advances and future directions. *IMAJ Isr Med Assoc J* 2009; 11: 753-7.
2. Samama MM. An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: the Sirius study. *Arch Intern Med* 2000; 160: 3415-20.
3. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; 361: 1139-51.
4. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009; 361: 2342-52.
5. Guyatt GH, Akl EA, Crowther M, Schunemann HJ, Gutterman DD, Zelman LS. Introduction to the Ninth Edition: Antithrombotic Therapy and Prevention of Thrombosis. 9th edn. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141: 48-52S.

Capsule

Actin filaments are recognized as danger signals

Besides responding to infections, the immune system can also recognize tissue injury in the absence of any infectious agents. Examples of this include antitumor immunity and responses to transplanted organs. During these "sterile" responses, the immune system is triggered by so-called DAMPs, danger-associated molecular patterns. These include intracellular contents such as ATP and HMGB1 that are released upon cell damage or death. The C-type lectin DNGR-1 (Clec9a) is a receptor expressed by certain subsets of dendritic cells that is required for the presentation of antigens derived from necrotic cells to T cells. What it recognizes on dying cells, however, has remained a mystery. After a rather challenging hunt, Zhang et al. and Ahrens et al. (*Immunity* 2012; 36: 635; 646) report that DNGR-1 recognized actin filaments. Monomeric actin, or G-actin, was not recognized by DNGR-1, and actin-binding proteins such as spectrin enhanced DNGR-1 recognition of actin. The identification of F-actin as a ligand for DNGR-1 reinforces the idea that molecules that normally play a housekeeping role in healthy cells are able to activate the immune system when released into the extracellular milieu. Although this often triggers a controlled immune response that promotes tissue repair, alterations in this response could drive inflammation and contribute to disease processes.

Eitan Israeli