EXCEPTIONAL CASE REPORT

blood advances

Rivaroxaban dose adjustment using thrombin generation in severe congenital protein C deficiency and warfarin-induced skin necrosis

Neethu Menon,[1] Ravi Sarode,[2] and Ayesha Zia[1]

[1]Division of Hematology/Oncology, Department of Pediatrics, and [2]Department of Pathology, The University of Texas Southwestern Medical Center, Dallas, TX

Key Points

- Rivaroxaban was efficacious and safe in a child with protein C deficiency to prevent the recurrence of skin necrosis or venous thrombosis.
- The dosage of direct oral anticoagulants in children with thrombophilia is unclear; a thrombin generation assay may be useful to adjust it.

Introduction

Congenital protein C (PC) deficiency is a strong thrombophilia characterized by uncontrolled thrombin generation (TG).[1,2] Secondary prophylaxis to prevent venous thromboembolism in PC deficiency consists of a long-term vitamin K antagonist.[1] However, warfarin lowers PC levels (half-life ~3 hours) rapidly before decreasing factors II and X (half life ~36-72 hours), leading to transient hypercoagulability that can cause skin necrosis at treatment outset.[3] Warfarin-induced skin necrosis (WISN) is rare but more likely to occur in severe PC deficiency.[4]

Rivaroxaban reversibly inhibits free and bound factor Xa and prevents the thrombin burst during the amplification phase of coagulation. It has predictable pharmacokinetic (PK) and pharmacodynamic (PD) properties and therefore does not require laboratory monitoring in adults.[5] Data regarding safety and efficacy in patients with strong thrombophilia are scarce, because such cases are excluded from most clinical trials. To overcome WISN during anticoagulation, dabigatran and rivaroxaban have been used successfully in adults with PC deficiency, and rivaroxaban has been used in a child with protein S (PS) deficiency.[6-8]

We report a case of severe PC deficiency in an adolescent treated with rivaroxaban after development of WISN. Physiologically, the thrombin-thrombomodulin complex activates PC; to preserve this natural anticoagulant mechanism, we preferred rivaroxaban to dabigatran in our patient.[7] We describe our experience of using a TG assay to guide rivaroxaban dosage.

Case description

A 13-year-old Hispanic girl, weighing 80 kg, presented with left lower extremity pain, swelling, and bluish discoloration without an underlying provoking factor. Doppler ultrasound revealed thrombosis involving the inferior vena cava, left external iliac vein, and popliteal vein. After catheter-directed thrombolysis and left iliac vein stent placement for May-Thurner syndrome, warfarin was initiated while concomitantly administering unfractionated heparin for 4 days. The patient was discharged once the international normalized ratio was >2 on 2 consecutive days. The patient returned 3 days later because of a tender hemorrhagic bullous lesion over the thigh. The international normalized ratio was 2.4, and PC activity from the initial presentation was <10% (supplemental Table 1). Findings of the remaining thrombophilia workup were negative. Warfarin was discontinued, and unfractionated heparin was initiated. She received vitamin K (2 mg) and fresh frozen plasma (6 mL/kg), but PC activity and antigen remained <10%, without any clinical improvement. PC concentrate (100 U/kg followed by 3 doses of 70 U/kg every 12 hours) led to near-complete resolution of the necrotic lesion within 4 days. PC activity and antigen levels rose to 171% and 183%, respectively. Anxiety related to subcutaneous shots precluded long-term use of low-molecular-weight heparin (LMWH), and 4 months later, she desired to switch to an oral anticoagulant. Rivaroxaban was started after obtaining written informed consent and assent. In the absence of any data regarding dosing at the time, we initiated rivaroxaban at 15 mg daily and titrated up weekly. Initially, the patient experienced tingling and burning in the resolved necrotic area. Based on PK, PD, and TG data, we increased the dose to 30 mg over 3 weeks, at which point she developed moderately severe nosebleeds and heavy menstrual bleeding leading to reduction of the

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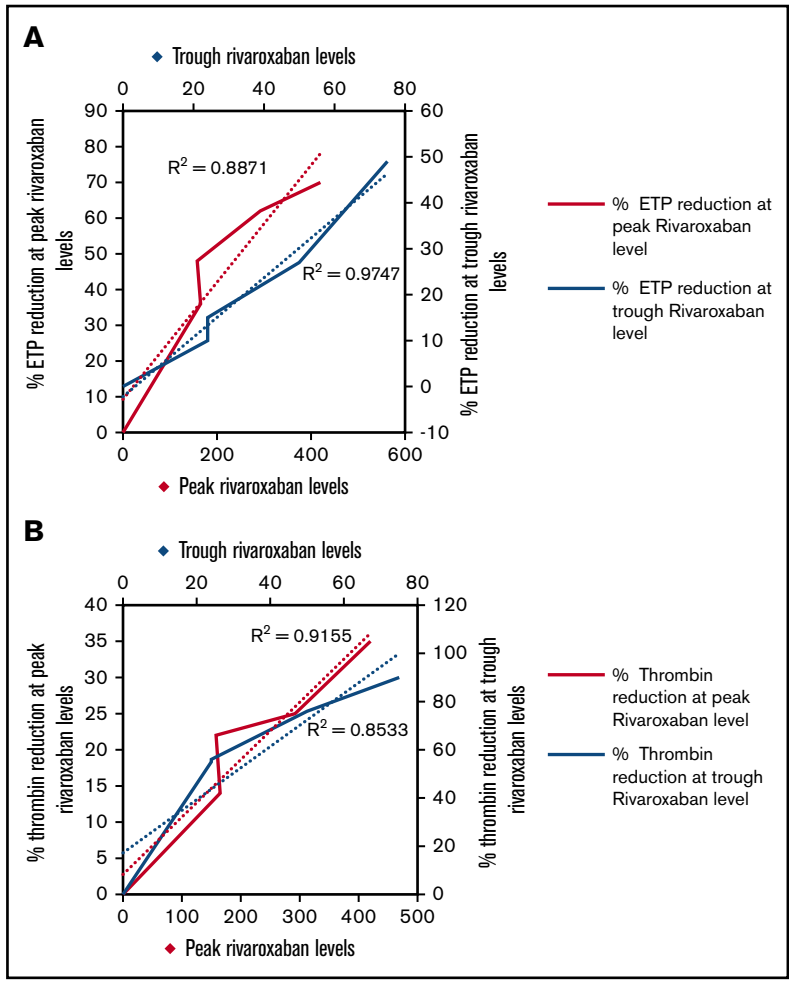

Figure 1. Positive correlation between rivaroxaban plasma levels and measures of thrombin generation. Positive correlation between rivaroxaban plasma levels and ETP (A) and thrombin peak (B) reduction at 15-, 20-, 22.5-, and 30-mg doses as measured by a TG assay.

dose to 22.5 mg daily (convenience dose based on 1.5 15-mg pills). She remains stable on this dose 3 years later without recurrence or bleeding.

Methods

Rivaroxaban monitoring

The anticoagulant effect of rivaroxaban was assessed via rivaroxaban plasma levels using a validated chromogenic anti-Xa assay (Biophen DiXal), prothrombin time (PT), activated partial thromboplastin time (aPTT), and a TG assay according to the method described by Hemker et al.[9-11] A dedicated software displays TG curves and calculates parameters, including area under the curve defined as endogenous thrombin potential (ETP; in nanomoles per minute) and thrombin peak (nanomoles).

Results and discussion

PK profile

Rivaroxaban plasma levels. Rivaroxaban peak levels 2 hours after the 15- and 20-mg doses were below the institutional peak ranges (Figure 1; Table 1) and trough levels were <30 μg/mL, at which point this test weakly correlates with the gold standard method of liquid chromatography-tandem mass spectrometry and is challenging to interpret accurately.[11] With 30 mg, the trough level increased and the peak exceeded the upper limit of the peak range. The 22.5-mg dose resulted in a peak and trough level within the on-therapy ranges reported for the 20-mg dose (Table 1).

PD profile

PT and aPTT. PT was 1.3 times the baseline after the 15-mg dose and ~2 times the baseline 2 hours after the 30-mg dose It returned to normal 24 hours after the dose at all dosages except the 30-mg dose, where it was minimally prolonged. aPTT also increased at peak levels of rivaroxaban, but it was not prolonged 24 hours after any of the 4 doses.

TG studies. We determined an ETP of 1900 nM·min and a thrombin peak of 400 nM as baseline, measured 24 hours after the last dose of LMWH. We aimed to find a dose of rivaroxaban that would decrease ETP and thrombin peak by at least 50% 2 hours postingestion based on previously determined ETP and thrombin peak values in age-matched healthy adolescent girls.[12] Thrombin peak decreased as desired with the 15-mg and 20-mg doses, but ETP reduction was only 36% and 48%, respectively. At 30 mg and clinical evidence of bleeding, there was 70% and 90% reduction in ETP and thrombin peak, respectively. A decrease in the dose to 22.5 mg decreased the ETP and thrombin peak by 62% and 76%.

Table 1. Patient's PK, PD, and TG profile at various doses of rivaroxaban

	Trough					Peak				
Dose, mg	Trough, μg/L	ETP, nM·min	Thrombin peak, nM	PT, s*	aPTT, s*	Peak, μg/L	ETP, nM·min	Thrombin peak, nM·min	PT, s*	aPTT, s*
15†	24	1700	344	14.1	32.8	165	1200	180	19.4	44.8
20†	24	1620	312	14.9	34.0	158	985	175	21.3	45.4
22.5‡	50	1375	300	14.0	34.4	292	715	95	24.4	48.6
30‡	75	1156	262	15.6	37.4	420	561	40	28.5	48.4

*Reference ranges for PT and aPTT are 12-15.3 seconds and 21.3-38.8 seconds, respectively.
†Reference ranges for rivaroxaban plasma levels were established for our center as follows: trough: 15 mg, 2-161 μg/L; 20 mg, 30-153 μg/L; peak: 15 mg, 180-480 μg/L; 20 mg, 182-408 μg/L.
‡No reference ranges are available for these doses.

This is the first report of successful use of rivaroxaban in a child with PC deficiency and WISN. Currently, many tests are used to measure rivaroxaban's effects, but they are limited by a lack of standardization.[13-15] Reference values for rivaroxaban plasma assays show wide ranges for trough and peak levels in different studies.[16] Whether keeping the levels within these wide ranges reflects a true rivaroxaban effect or simply reflect "on-therapy" levels in a patient with strong thrombophilia is unclear. TG has been shown to be a sensitive tool to describe the PD effects of various anticoagulants.[17-20]

In our patient, the 15- and 20-mg doses decreased peak thrombin levels effectively by more than 50%, but not ETP. The reduction of thrombin peak was more than that of ETP for all doses at peak rivaroxaban levels, suggesting that thrombin peak may be more sensitive regarding the PD effect of rivaroxaban than ETP, as previously reported.[21] The level of ETP reduction was low compared with what has been described in the literature.[22] Variations in the plasma content of pro- and anticoagulant factors or other proteins such as albumin or fibrinogen, which are known to affect the PD effects of other anticoagulants, are likely at play.

A rivaroxaban dose of 40 mg divided 4 times daily was necessary to prevent recurrence of skin necrosis in a child with PS deficiency and WISN.[7] In contrast, our patient did not experience similar recurrences of skin necrosis at lower doses. The PK profile of the PS-deficient patient demonstrated rivaroxaban levels <25 μg/L 8 hours after a 10-mg dose, whereas our patient had a trough level of 50 μg/L 24 hours after the 22.5-mg dose. These findings suggest that a higher and more frequent dosage may be required at a younger age due to faster clearance.

We would like to highlight some limitations. The addition of thrombomodulin to TG assessment may have provided mechanistic insight into the effects and variability, if any, of rivaroxaban on the PC and PS pathways. This was only available for the 22.5-mg dose, and as such, no conclusion can be drawn from it. TG was analyzed after a washout period off LMWH, so the magnitude of her true hypercoagulability is unknown. Lastly, TG was analyzed only once for each dose (except 22.5 mg); however, the intraindividual variation in ETP and thrombin peak is only 4.5% and 5.5%, respectively, and therefore unlikely to have affected our results substantially.[9] At the 22.5-mg dose, the TG test was measured twice with a variation of $<5\%$ in the ETP and peak.

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Authorship

Contribution: N.M. drafted the paper and analyzed data; R.S. reviewed and edited the paper; and A.Z. designed research, analyzed data, and edited the paper.

Conflict-of-interest disclosure: R.S. serves as a consultant for CSL Behring and Octapharma. A.Z. has received honoraria from Shire and Octapharma in an advisory capacity. N.M. declares no competing financial interests.

ORCID profiles: A.Z., 0000-0003-3283-0415.

Correspondence: Ayesha Zia, The University of Texas Southwestern Medical Center, Division of Hematology/Oncology, 5323 Harry Hines Blvd, Dallas, TX 75390; e-mail: ayesha.zia@utsouthwestern.edu.

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