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Major bleeding under enoxaparin treatment. An unexpected second offender

Abstract

Admitted to hospital with an ischemic stroke, a 63-year-old male was diagnosed with a left ventricular mural thrombus. Enoxaparin treatment was started. Over 6 weeks there were two episodes of major hemorrhage needing brief discontinuation of anticoagulation. A previously normal prothrombin time (PT) became prolonged upon which vitamin K deficiency was diagnosed. The deficiency was caused by enteral feeding using a formula which did not contain the required daily dose of vitamin K. A triple message emerges from this observation: theneed for monitoring the PT in patients receiving enteral feeding, more so in those receiving anticoagulant along with enteral feeding, and the appeal to fortify feeding formulas with vitamin K.

Keywords: vitamin K, enteral feeding formula, prothrombin time, enoxaparin, major bleeding

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Introduction

Long-term anticoagulant treatment is a must in patients with a left ventricular mural thrombus. The toll of major bleeding associated with anticoagulation is acceptable in considering the benefit. This was shown in a large prospective study of patients with left ventricular mural thrombus. Anticoagulation was provided mainly with vitamin K antagonists (48.4%), DOACs (22.6%), and low molecular weight heparin (23.3%). Concomitant antiplatelet therapy was given to 67.9% of patients. During a median follow-up of 632 days there was 18.9% mortality, 13.3% stroke and 13.2% major bleeding (1). In our latest experience, a patient admitted for rehabilitation after an ischemic stroke, left ventricular mural thrombosis, receiving enoxaparin treatment had repeatedly major hemorrhage. Aprogressive prolongation of prothrombin time (PT)was noticed and lessof the activated partial thromboplastin time(APTT).The cause of the acquired coagulation disorder was not apparent at the beginning.

Case history

A 63-year-old male, working as a computer technician, with a long history of arterial hypertension, ischemic heart disease, dyslipidemia, was active and hard working until recently. He had neglected to present on medical follow-up and was taking his medications irregularly. Two months after a recent transient ischemic attack he presented to hospital with dizziness, vomiting and numbness in the right arm and right leg. CT angiography revealed complete obstruction of the left vertebral artery, segment 4, which was inappropriate for endovascular treatment. The electrocardiogram showed atrial fibrillation and poor progression of r waves in precordial leads V1-V4. Transthoracic echocardiography revealed apical akinesia, LVEF 40% and an apical left ventricular mural thrombus. Enoxaparin treatment was started 1mg/kg body weight b.i.d. After the initial surge of the blood pressure, measurements returned to normal, and antihypertensive medications were discontinued. Atorvastatin 80mg/day was instituted. In diagnosing severe oropharyngeal dysphagia which precluded oral intake, enteral feeding was instituted with Osmolite® 1400mL/day.

Two episodes of major bleeding ensued (Figure 1). The first occurred two weeks after the stroke: a hematoma contained within the sheets of the right biceps muscle 6.6x3.5x5cm in size. There was no history of trauma to the arm. Enoxaparin treatment was withheld for 5 days. A second incident of major bleeding occurred 4 weeks later, at this time the hematoma extending along the left thigh and calf.

Laboratory tests showed normal CBC, serum creatinine 1.3mg/dL, BUN 24mg/dL. Intriguing were the late results of prolonged PT and APTT, not present at the time of admission, and subsequently corrected by administration of 10mg vitamin Kintravenously (Table 1).

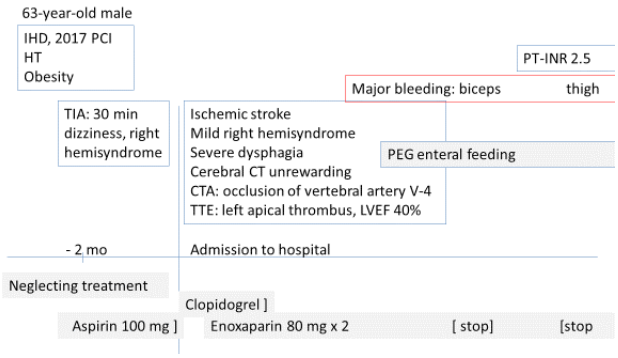

Figure 1 Summary of the patient history.

On the same day the patient received vitamin K he complained of pain in the left hip and thigh. No abnormality or limitation of movement was found on examination. The next day, however, the pain became worse along with numbness in the thigh. A large hematoma discolored the skin of the thigh which became swollen and firm on palpation. Enoxaparin treatment was discontinued. With evidence of major bleeding and finding early signs of compartment syndrome the patient was referred to hospital. The hemoglobin had decreased by 3gram/dL. The outcome was favorable: the surgical consultant countered the diagnosis of compartment syndrome. The patient was admitted for observation and adjustment of treatment.

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Table 1 Time sequence coagulation tests and treatment

Date	PT INR (0.9-1.2)	PT seconds (9.4-13.6)	APTT seconds (25-37)	Medication
6.2020	1.02			Clopidogrel
11.3.2021	1.19	14.2	39.5	Enoxaparin
19.3.2021	1.32	15.9	39.2	Enoxaparin
11.4.2021	2.5	33.5	52	Enoxaparin
13.4.2021	2.3	31.7	48.7	Enoxaparin
16.4.2021	1.1	14.1	30.7	Vitamin K, Enoxaparin

Discussion

A prolonged prothrombin time may be caused by several conditions: reduced hepatic synthetic function, congenital deficiency of clotting factors, vitamin K deficiency (vitamin K is required for normal functioning of factors II, VII, IX, X), disseminated intravascular coagulation, and by inhibitors of coagulation factors II, V, X. Concomitant prolongation of the PT and APTT is consistent with liver failure, vitamin K deficiency, warfarin treatment, factors II, V or X deficiency, amyloid adsorbed factor X, or presence of a specific coagulation factor inhibitor.[1] In this patient's clinical context there were two main considerations: vitamin K deficiency recently acquired, and presence of a coagulation factor inhibitor. Vitamin K deficiency was identified by correcting the PT and APPT by administration of vitamin K.[2]

Vitamin K is obtained from green vegetables and by bacterial synthesis in the gut. Vitamin K is essential for the posttranslational gammacarboxylation of clotting factors II, VII, IX and X (and the natural anticoagulants protein C and protein S); in the absence of vitamin K, these factors are released from the liver in a non-functional form. As a result the PT is particularly prolonged. A coagulopathy due to vitamin K deficiency occurs when absorption is defective, particularly in obstructive jaundice where bile cannot reach the duodenum.[3] Also patients who undergo major malabsorptive (bariatric) surgeries are at risk of developing vitamin K deficiency. At this point, it is still unclear whether supplementation of vitamin K is required, and what oral dose or vitamer type should be used to normalize serum levels after different types of bariatric procedures.[4] Patients receiving enteral nutrition or total parenteral nutrition may develop vitamin K deficiency. The requirements of Food and Drug Administration for an effective adult parenteral multivitamin drug product specify inclusion of 150microg of vitamin K.[5] A study compared the micronutrient content of the most common enteral nutrition formulas with European dietary reference values (DRVs) for healthy population. Sixty-two nutritionally complete enteral formulas were considered. It was shown that daily vitamin K requirements were not covered by any of the analyzed enteral nutrition formulas.[6] Osmolite, which the proposito was receiving, contains 61 mcg vitamin K per 1000 mL. In receiving during 30days of enteral feeding 1400mL of Osmolite, the patient became depleted of vitamin K. Indeed, one notable feature of vitamin K metabolism is that it is poorly retained in the body. Studies with [3H]-labeled phylloquinone indicated that 60–70% of doses in the range of 45–1000microgram of vitamin K1 were excreted within 5 days.[7] While by itself enoxaprain may increase the PT INR,[8] a fact usually not given importance, this did not occur in the proposito. In this particular case, vitamin K deficiency was the major cause of alteration of the coagulation tests.

Vitamin K deficiency occurred under prolonged enteral feeding that did not supply the daily vitamin K requirement. Anticoagulant treatment combined with defective synthesis of coagulation factors under vitamin K deficiency were responsible for the latest major bleeding event. At the time vitamin K was administered bleeding had already begone, but was occult and unrecognized. So, correction of the PT and APTT were too late for preventing bleeding.

In conclusion, there may be an unrecognized, at present, need for monitoring the PT in patients receiving enteral feeding. This is even more important inpatients receiving anticoagulant treatment along with enteral feeding. The present case endorses the appeal to fortify feeding formulas with vitamin K.

Conflicts of interest

The author declares no conflict of interest.

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