Prolonged PT

3

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Introduction

It is unusual for "prolonged PT" to be the reason for a consult. More commonly, both PT and PTT are prolonged, or isolated PTT elevation is more common because there are more reasons for an elevated PTT compared with PT.

Remembering back to the coagulation cascade, the PT measures the extrinsic system. Factor VII is cleaved by tissue factor to act on factor X, in order to activate factor X. The primary reason why there would be an isolated PT prolongation usually involves a deficiency of, or rarely, an inhibitor to factor VII.

Clinical Vignette

You are asked to see a patient in the SICU, who is having some infectious problems after a routine cholecystectomy. She is a 54-year-old woman, who had normal coagulation tests (PT, PTT, and fibrinogen, as well as platelet count) prior to surgery. The cholecystectomy was done because of symptomatic stones, yet was done electively.

Post-op, amylase and lipase were normal, but she developed a wound infection and had positive blood cultures for Gram-negative rods and a brief episode of hypotension, for which she was on dopamine for less than 12 h. She had prolonged nausea and vomiting and was not eating or drinking, as well as being on IV antibiotics.

Six days into the admission, routine labs were drawn, and the prothrombin time was now 19 s, with INR of 1.9, PTT normal, complete blood count and differential showed WBC 12,100, with slight left shift, hemoglobin 10.9 g/dL, and platelets 456 k/μL. Her fibrinogen was 645 mg/dL.

The reason you are being asked to see her is the prolonged prothrombin time.

You order a mixing study, and it corrects, suggesting a factor deficiency.

You order a factor II, V, VII level, and they return with a factor II level of 19 %, factor V of 121 %, and factor VII level of 16 %. You feel the most likely cause of these numbers is vitamin K deficiency and recommend the surgical team give her vitamin K, which she receives as 5 mg IV without any untoward incident. By 48 h after you've seen her, she is improved, with better oral intake, and the prothrombin time has normalized.

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The PT Measurement

This material is covered in Chap. 1, but repeating it here will be helpful.

Historically, the PT was performed by adding tissue factor to citrated chelated, hypocalcemic plasma. The tissue factor was derived from brain tissue and acted as a thromboplastin or phospholipid complex. The tissue factor would interact with the activated factor VII in the plasma and activate the extrinsic cascade. The term extrinsic arose because the thromboplastin or tissue factor was outside of the normal flow of blood within the blood vessels. The PT also gives an indication of the activity of the clotting factors in the common pathway factors X, II and V, as well as fibrinogen.

The PT will be variably prolonged depending upon how low the factors VII, X, V, and II and fibrinogen concentrations are. This variability is different for each one of these factors. Also, the height of the PT value does not correlate linearly with the factor concentrations, so it can remain in the normal range with mildly depressed levels of some of these factors.

Up until the 1990s, different labs, in different countries, using different tissue factor sources would report out PTs in units of "seconds" to coagulate the plasma. Comparing studies on each side of the Atlantic gave disparate answers to clinical questions related to warfarin dosing so, by convention, laboratories developed the International Normalized Ratio, or INR, to standardize the PT results. A formula used by reagent companies and labs was developed.

Patient PT ^{ISI}

INR: Control PT

ISI stands for International Sensitivity Index and is calculated for each batch of tissue factor containing material. INR should only be used for monitoring warfarin (Kitchen and Preston 1999). It is not a reliable way to monitor liver function because the way it is calculated is based on plasma from patients taking warfarin.

Table 3.1 Causes of prolonged prothrombin time (PT)

Congenital
Factor VII deficiency
Acquired
Vitamin K deficiency
Coumadin use
Disseminated intravascular coagulation
Liver disease
Factor VII inhibitors

It is possible to observe a shortened PT. If the tube the blood is drawn in is not properly siliconized or if excessive activation of coagulation occurs in the tube, such as what can occur with a venipuncture that is excessively traumatic, one may have a PT that is shorter than the normal range. It should also be remembered that elevated levels of factor VII, prothrombin, and fibrinogen may lead to a thrombotic tendency, but the PT may remain in the normal range (Table 3.1).

Factor VII

Factor VII sits in a unique position in the extrinsic cascade, since it alone can activate the common pathway once it comes in contact with tissue factor.

Once one gets a consult for a prolonged PT, the next step is performing a mixing study. If there is correction of the PT by mixing a patient's plasma 1:1 with normal plasma, one knows one is dealing with a deficiency of a clotting factor, and the most likely clotting factor deficiency in this setting would be factor VII. If, on mixing, there continues to be prolongation of the PT, one may be fairly certain that there is an inhibitor to a clotting factor and factor VII inhibitors can occur, though they are rare.

Congenital factor VII deficiency is rare, as well, only occurring in 1/500,000 people (Gailani and Neff 2008). Factor VII deficiency is inherited as an autosomal recessive defect. Factor VII deficiency is usually due to an abnormally low level of factor VII function. There are some factor VII-deficient individuals who have a discordant deficiency of activity compared to antigenic levels of

factor VII (Coyer et al. 1997; Sabater-Lleal et al. 2003). Factor VII-deficient individuals can have an unpredictable story for bleeding compared with level of activity. Factor VII levels of around 20 % are adequate for hemostasis with surgery. Severe factor VII deficiency with levels <1 % is usually associated with spontaneous bleeding, like bruising, epistaxis, menometrorrhagia, and soft tissue bleeding. Some severe factor VII-deficient individuals can have hemarthroses and intracranial hemorrhage, as can be seen in factor VIII and factor IX severe deficiency. Interestingly, there are some individuals with severe factor VII deficiency with levels <1 % who have no bleeding history (Mariani et al. 2005; Girolani et al. 2007). This might be because the source of the reagent to calculate the PT and factor VII level might yield different results. Bovine and rabbit thromboplastin will give lower values than when human thromboplastin is used as a source for tissue factor in assays of factor VII activity (Roberts and Escobar 2002).

When one is called to see someone with a prolonged PT and once a mixing study demonstrates a clotting factor deficiency and the coagulation lab tells you there is a deficiency of factor VII, one must decide if this is congenital or acquired. Lifelong history of bleeding can lead one to suspect a congenital deficiency. Obtaining old lab data and finding that the PT was always prolonged also is evidence for a congenital deficiency. If one sees that old PTs were normal and now are prolonged, this is evidence for an acquired deficiency.

The most common reasons for an acquired factor VII deficiency are vitamin K deficiency (either because of warfarin use or not) and liver disease. There are some other rare problems that have been associated with factor VII deficiency, such as aplastic anemia (Weisdorf et al. 1989), homocystinuria (Dantzenberg et al. 1983), Dubin–Johnson (Seligsohn et al. 1969), and Gilbert syndrome (Seligsohn et al. 1970).

Vitamin K—The discovery of vitamin K in the 1930s by Dam and Glavind (1938) ushered in a new era of understanding of the biochemistries of blood clotting. Bleeding disease in cattle ("sweet clover disease of cattle") was found to be due to coumarols, which interfered with vitamin K dependent synthesis of prothrombin.

Vitamin K is formed by intestinal flora bacteria (Hill 1997). It is a cofactor in the posttranslational gamma-carboxylation of glutamic acids in several procoagulants, as well as for natural anticoagulants (Furie et al. 1999). Vitamin K is involved in the conversion of inactive factors II, VII, IX, and X into gamma-carboxylated forms of these procoagulants. Once gamma-carboxylated, a stable divalent anion is formed, which allows for calcium ions to bind and thus localize these clotting factors to phospholipid membranes. They also cause formation of internal calcium channels.

The vitamin K molecule undergoes chemical changes as the gamma-carboxylation process occurs. The hydroquinone is converted to an inactive vitamin K epoxide as the gamma-carboxylation takes place. Vitamin K epoxide is reduced back to an active hydroquinone by vitamin K epoxide reductase, which regenerates more vitamin K to permit further gamma-carboxylation (Ageno et al. 2012). See Fig. 3.1.

Patients may become vitamin K deficient by poor oral intake, antimicrobial use (eradicating gut flora), intestinal disorders that interfere with absorption of fat-soluble vitamins, and biliary tract disorders that lead to impaired bile acid levels entering into enterohepatic circulation. Once vitamin K levels fall, there is less gamma-carboxylation of factors II, VII, IX, and X. Because factor VII has the shortest half-life of all the clotting factors, oftentimes early vitamin K deficiency may cause an isolated elevation of the PT and not the PTT. Thus, any patient whose initial PT was normal on entering the hospital and who develops a prolonged PT in the hospital likely is vitamin K deficient.

When a patient is on warfarin, frequent consults have to do with (1) reversal of prolonged PT because of bleeding, (2) management of the warfarin during a bridging process to allow for surgery to occur, or (3) increased or decreased sensitivity of the patient to warfarin.

Giving vitamin K IV or subq can cause anaphylaxis (Fiore et al. 2001), usually to the

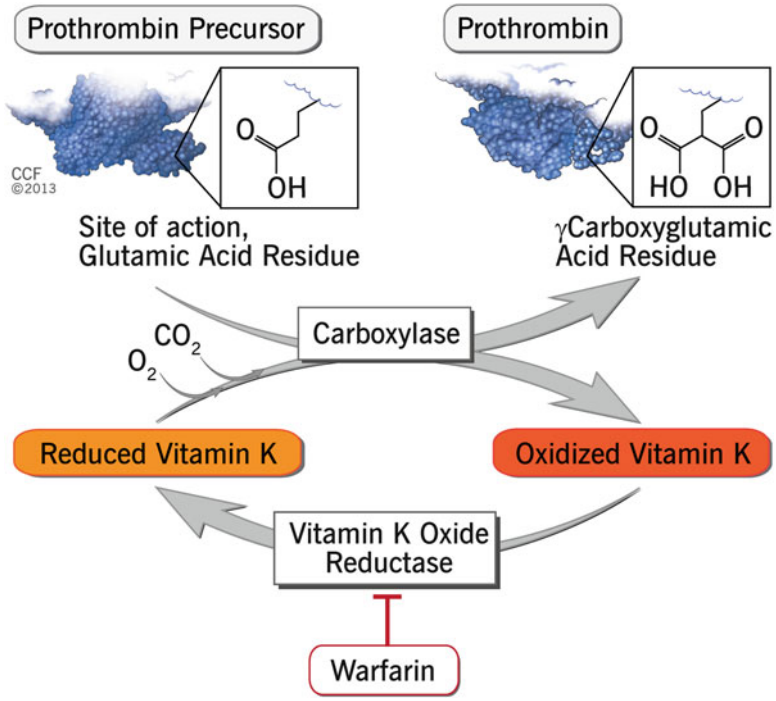

Fig. 3.1 The mechanism of "oxidized vitamin K" reduction by vitamin K oxide reductase and its inhibition by warfarin. The goal of this vitamin K cycling is the gamma-carboxylation of factors II, VII, IX, and X

cremophor part of the preparation. This is more likely to occur in elderly patients who receive >5 mg or after repeated dosing but can occur in young patients too. For IV administration, it is advised to mix the vitamin K in 100 mL of saline and administer it carefully over 20 min and to abort the infusion if any flushing or hypotension is seen (Patriquin and Crowther 2011).

When a patient has a thrombosis and is on heparin and then needs to be converted to oral warfarin, a frequent consult, as stated, is that some patients after one or two doses of warfarin suddenly have INR > 9 and then others do not budge their INR above 1, even after several days of fairly high-dose warfarin. This can be because of several different mechanisms, related to concurrent other medications, endogenous metabolism of warfarin, coincident early vitamin K deficiency, or variation in activity of the enzymes involved in vitamin K metabolism.

Pharmacogenomics and Warfarin Sensitivity or Resistance

Much has been written over the past 10 years about genetic polymorphisms that can predict how a person will metabolize warfarin, as well as other drugs (Kitzmiller et al. 2011). There are two of these with the greatest clinical relevance to warfarin metabolism: (1) cytochrome P-450 2C9, or CYP2C9, and (2) vitamin K epoxide reductase complex 1 (VKORC1).

The first of these, the hepatic cytochrome P-450 2C9, is involved in the inactivation of warfarin (Shikata et al. 2004). There are two isomers of warfarin, S-warfarin and R-warfarin. S-warfarin is the more potent of the two. S-warfarin is metabolized mostly by CYP2C9, and R-warfarin is metabolized by other cytochrome P-450 polymorphisms, mainly the CYP1A2, CYP2C19, and CYP3A4.

Those individuals with two copies of the wild-type CYP2C9 gene (CYP2C9*1) are "extensive warfarin metabolizers" and clear warfarin from the plasma very rapidly. Others, such as the allelic variants CYP2C9*2 and CYP2C9*3, may metabolize warfarin at rates up to 90 % lower (Au and Rettie 2008). Doses of warfarin to keep individuals in a specific therapeutic range may be based on these genotypes (Taube et al. 2000). Different ethnic groups also have varying genetic expression of these cytochrome P-450 variants. For example, Caucasians carry at least one copy of CYP2C9*2 eight times more frequently than African Americans, and the ratio for CYP2C9*3 is 6:1. Caucasians harbor this latter genetic allele twice as often as Asians (Garcia-Martin et al. 2006).

The other well-studied genetic variable is vitamin K 2,3-epoxide reductase (VKOR). Polymorphisms of the gene encoding the C1 subunit of VKOR, the VKORCI, affect the level of inhibition of warfarin (D'Andrea et al. 2005). These individuals with a single nucleotide polymorphism 1,639 bases upstream of VKORC1 (−1,639 G > A) need 25 % of a lower dose of warfarin than other genotypes. Groups have identified ten noncoding VKORC1 single nucleotide polymorphisms and inferred five major haplotypes. There was a low-dose haplotype group (A) and a high-dose haplotype group (B). There were significant differences between the dose of coumadin necessary to keep these different groups in a therapeutic range. Again differences in ethnicity dictated different rates of A and B haplotypes (Rieder et al. 2005).

Studies have also shown that, based on genotype, there are differences in the rapidity of rise of the PT (time to the first INR in the therapeutic ranges), time to first INR > 4, and the overall average dose of warfarin after 29 days.

Despite all the genetic information and despite the FDA approving the commercialization of kits to identify these SNPs, the American College of Chest Physicians CHEST guidelines in 2012 still do not endorse the use of genetic typing of individuals prior to initiating warfarin or for maintaining warfarin doses over a long time. The Center for Medicare and Medicaid Services (CMS) "believes that the available evidence does not demonstrate that pharmocogenomic testing of CYP2C9 or VKORC1 alleles to predict warfarin responsiveness improves health outcomes in Medicare beneficiaries". There are some provisions under which this testing might be covered, such as when the individual has had less that 5 days of warfarin therapy and if the individual is enrolled in a clinical trial examining this issue.

One setting in which knowing the genetic typing might be helpful is in determining the cause for an individual's either extreme sensitivity or extreme resistance to warfarin. When a clinician is not certain why a patient seems to need a dose of warfarin of 30 mg or more per day to nudge the INR up to 2.0 and one is suspecting that maybe the patient is just not taking his or her warfarin, knowing they harbor a SNP that dictates for resistance to warfarin may be reassuring and improve the doctor–patient relationship.

Factor VII Inhibitors

Once the consultant is called for a prolonged PT evaluation and a 1:1 mix is ordered and done and the coagulation laboratory reports the presence of an inhibitor, the consultant needs to ask the coagulation laboratory to do further testing to see if there is a specific inhibitor to factor VII. Delayed inhibition in the 1:1 mix would likely indicate a factor VII inhibited patient. These are very rare (Delmer et al. 1989; Mullighan et al. 2004). Quantifying the level of factor VII inhibitor (Bethesda titer) sometimes can guide therapy. Generally, replacing factor VII with fresh frozen plasma or recombinant VIIa may cause an anamnestic response with the development of even higher titer of inhibitor. Plasma exchange and immunosuppressants have been used in these patients with variable response.

Treatment of Factor VII Deficiency

If the 1:1 mix demonstrates a deficiency of factor VII and bleeding is occurring or surgery is being contemplated, one may choose to replace factor

VII with fresh frozen plasma, or recombinant factor VIIa may be used (Lusher et al. 1998). Factor VII levels of 5–10 % may be all that is necessary to stop bleeding. Levels of around 20 % are adequate for most surgeries.

Since factor VII has a short half-life, a single dose of 20–30 micrograms (mcg) recombinant factor VIIa/kg body weight may be enough to stop bleeding. For more significant bleeding, Factor VIIa at doses up to 20–50 mcg/kg every 2–6 h for a few days may be necessary. The doses for recombinant VIIa used in factor VIII or IX inhibitor patients who are bleeding or who need surgery may be as high as 90 mcg/kg every 2 h for several days.

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