# Warfarin Initiation and Monitoring with Clotting Factors II, VII, and X

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**OBJECTIVE:** To report a case of a patient with antiphospholipid antibody syndrome and multiple thromboses who developed heparin-induced thrombocytopenia (HIT) and subsequent international normalized ratio (INR) prolongation possibly due to antiphospholipid antibodies.

**CASE SUMMARY:** A 56-year-old white woman with a history of antiphospholipid antibody syndrome and thrombosis taking chronic warfarin was admitted for gastrointestinal concerns and found to have an INR >14. Warfarin was discontinued, vitamin K was administered, and a heparin infusion was initiated. Over the next 2 days, thrombocytopenia, hypotension, tachycardia, hyponatremia, and progressive abdominal pain developed. Upon transfer to a tertiary care center, HIT was diagnosed, and a lepirudin infusion was initiated. Subsequently, a sudden elevation of the INR occurred (>14) with low prothrombin (factor II) activity. After INR values declined to 2–3, warfarin was reinitiated with dosing adjusted using factor X and II activity levels. Clotting factors II and X activities were measured to monitor long-term warfarin therapy, with no evidence of complications after 7 months.

**DISCUSSION:** Typically, the INR is used to assess the intensity of anticoagulation. The INR value represents the reduction of clotting factors II, VII, and X. In rare circumstances, an independent inhibitor or interfering substance can interfere with the process of measuring the INR. In such situations, an alternative approach can be direct measurement of clotting factor concentrations.

**CONCLUSIONS:** Factor II and/or factor X activity levels provided an alternative means for measuring the anticoagulant effects of warfarin in the presence of a significant inhibitor (antiphospholipid antibodies) that biased the INR measurements.

**KEY WORDS:** factor II, factor VII, factor X, heparin-induced thrombocytopenia, international normalized ratio, lepirudin, monitoring, warfarin.

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Active thromboembolism is usually managed acutely with either unfractionated heparin (UFH) or a low-molecular-weight heparin (LMWH) followed by warfarin. If heparin-induced thrombocytopenia (HIT) is present, then traditional initial therapy with UFH or LMWH must be avoided and a direct thrombin inhibitor (DTI) is initiated, usually followed by warfarin once the platelet count has recovered. The intensity of warfarin's anticoagulation effect is primarily measured using the international normalized ratio (INR), which reflects the reduction in vitamin K–dependent clotting factors II, VII, and X.[1] On rare occasions, antibodies or inhibitors, such as antiphospholipid antibodies or lupus anticoagulants, can interfere with INR determinations, making it more difficult to assess the degree of vitamin K–dependent clotting factor reduction.

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We describe a case of a patient requiring long-term anticoagulant therapy who developed recurrent thrombosis followed by HIT.

## Case Report

A 56-year-old white woman with a history of antiphospholipid antibody syndrome (APS) was receiving chronic warfarin therapy secondary to recurrent strokes. Other relevant medical history included depression, hypertension, anemia, and seizure disorder. She was admitted to the hospital for increasing abdominal pain, dehydration, and a 2-week history of diarrhea refractory to loperamide. A colonoscopy was done, and *Clostridium difficile* pseudomembranous colitis was eventually diagnosed, which was treated with oral vancomycin. The patient subsequently developed severe bilateral abdominal pain. An abdominal computed tomography (CT) scan was unremarkable. A repeat CT was questionable for adrenal hemorrhage, which was subsequently ruled out. At the time of admission, the patient's INR was >14. Warfarin was withheld, and the INR was reversed with vitamin K. Platelets were $189 \times 10^3/mm^3$ (normal 130–400). Due to the patient's risk for thrombosis, a heparin infusion was initiated. Within 48 hours after starting heparin, the patient became

thrombocytopenic (platelets $35 \times 10^3/mm^3$), hypotensive, tachycardic, and hyponatremic, and developed worsening abdominal pain requiring transfer to a tertiary care medical center.

At transfer (transfer day 1), the platelet count was $38 \times 10^3/mm^3$, INR 1.38, and serum creatinine 2.1 mg/dL. Because HIT was highly suspected, heparin was discontinued and lepirudin initiated with a 0.4-mg/kg bolus dose followed by a continuous infusion of 0.05 mg/kg/h (reduced dose secondary to renal insufficiency) targeting an activated partial thromboplastin time (aPTT) between 50 and 70 seconds (Table 1). An enzyme-linked immunosorbent assay for platelet factor 4-heparin antibodies gave a highly positive result. Warfarin was initiated with low doses of 2 mg/day given intravenously to gradually bring the patient's INR back into the therapeutic range (prior history had been 7.5 mg/day alternating with 5 mg/day). After 2 warfarin doses, the patient's mental status became altered, and warfarin was withheld for several days to rule out intracranial hemorrhage. No evidence of intracranial hemorrhage was found, but lower extremity ultrasound indicated a right upper extremity deep vein thrombosis. On transfer day 6, the patient became hypotensive, tachypneic, and tachycardic, and was transferred to the intensive care unit (ICU) with concern for sepsis and intubated secondary to respiratory distress. Pulmonary embolism was ruled out.

While in the ICU, lepirudin was continued at doses between 0.03 and 0.07 mg/kg/h to maintain the aPTT between 50 and 70 seconds (serum creatinine 2.1–2.4 mg/dL). A repeat antiphospholipid antibody test was highly positive for immunoglobulin G and M isotypes. The INR was 1.86; the presence of an inhibitor that interferes with the INR assay to prolong the time to form a clot was suggested when the mixture of patient's plasma to pooled normal plasma failed to completely correct the INR. The D-dimer was 7.2 (normal 0–1.5) and the fibrin monomer test was negative. On transfer days 12 and 13, multiple INR measurements >14.7 were observed. A finger-stick–derived sample for an INR using a Coagucheck (Roche Diagnostics) INR monitor showed similar results. Intravenous vitamin K 1.5 mg was administered to correct the prolonged INR. The lepirudin infusion was temporarily withheld due to concerns over the patient's high INR and bleeding risk. To assess for possible presence of clotting factor consumption, undetected liver insufficiency, or vitamin K pathway impairment, the vitamin K pathway clotting factors II and VII and the non–vitamin-K pathway clotting factor V were

**Table 1.** Clinical Course

| Transfer Day | Platelets ($\times 10^3/mm^3$) | aPTT (sec) | INR | Factor II[a] (IU/mL) | Factor VII[a] (IU/mL) | Factor X[a] (IU/mL) | Warfarin | Comment |
|---|---|---|---|---|---|---|---|---|
| 1 | 38 | 26 | 1.38 | | | | | start lepirudin |
| 2 | 46 | 61 | | | | | 2 mg iv | |
| 3 | 61 | 67 | 1.73 | | | | 2 mg iv | |
| 4 | 55 | 65 | 1.8 | | | | | |
| 5 | 70 | 63 | 1.95 | | | | | |
| 8 | 38 | 68 | 2.29 | | | | | |
| 10 | 62 | 73 | 3.12 | | | | | |
| 11 | 77 | 76 | 3.52 | | | | | vitamin K 0.5 mg iv |
| 12 | 87 | 82 | >14 | | | | | vitamin K 1.0 mg iv |
| | | 82 | >14 | | | | | |
| 13 | 101 | 89 | >14 | | | | | |
| | | 101 | >14 | | | | | |
| 14 | 109 | 75 | >14 | ND | 0.64 | | | D-dimer 2.9 DRVVT 84 sec, factor V 0.64 IU/mL |
| 15 | 113 | 64 | 5.24 | ND | 0.78 | | | DRVVT 104 sec, factor V 0.79 IU/mL |
| 16 | 108 | 60 | 2.42 | 0.07 | | 0.52 | | |
| 22 | | 49 | 2.04 | | | | | vitamin K 5 mg po × 3 |
| 30 | 185 | 63 | 2.6 | 0.53[b] | | 0.90[b] | | factor V 1.06 IU/mL |
| 33 | | 68 | 2.6 | 0.53 | | 0.85 | | factor V 0.79 IU/mL |
| 41 | | 83 | 2.8 | | | | 5 mg | all additional warfarin doses given po |
| 42 | 155 | 72 | 2.3 | 0.45[c] | | 0.68[c] | 3 mg | |
| 43 | 159 | 67 | 2.4 | | | | 3 mg | |
| 44 | 169 | 63 | 2.3 | 0.46 | | 0.66 | 3 mg | |
| 45 | 187 | 65 | 2.3 | | | | 5 mg | |
| 46 | 208 | 71 | 2.8 | | | | 5 mg | |
| 47 | 191 | 66 | 2.4 | | 0.43[d] | | 5 mg | |
| 48 | 189 | 58 | 4.6 | | 0.41 | | 5 mg | |
| 48 | 186 | 53 | 2.5 | | 0.56[e] | | 3 mg | |
| 50 | 201 | 48 | 2.2 | | | | 7.5 mg | |
| 51 | 201 | 54 | 3.3 | | 0.26 | | 7.5 mg | |

aPTT = activated partial thromboplastin time; DRVVT = dilute Russell's Viper Venom test; INR = international normalized ratio; ND = not determined.
[a]0.1 IU/mL = 10%; unless noted, all factor levels were drawn during lepirudin infusion.
[b]Factor level drawn 6 hours after lepirudin held.
[c]Factor level drawn 24 hours after lepirudin held.
[d]Factor level drawn 8 hours after lepirudin held.
[e]Factor level drawn 18 hours after lepirudin held.

measured. The results showed factor II 0.07 IU/mL (normal 0.50–1.50), factor V 0.64 IU/mL (normal 0.50–1.50), and factor VII 0.64 IU/mL (normal 0.50–1.50).

The Dilute Russell's Viper Venom test (DRVVT) suggested a potential lupus anticoagulant, which was thought to be interfering with the INR results. As such, warfarin was still withheld, and the lepirudin infusion was continued to maintain the aPTT between 50 and 70 seconds. In the absence of warfarin, the INR persisted between 2.5 and 2.8 and additional oral vitamin K 5 mg was given daily for 3 days (transfer days 22–24). On transfer day 30, the patient's factor II levels had recovered to 0.53 IU/mL.

Warfarin was restarted on transfer day 41 targeting a gradual increase to reduce the risk of venous limb gangrene associated with overanticoagulation and concurrent INR values above the target range in the presence of HIT.[2] The patient's warfarin response was initially measured using factor VII activity levels followed by factor II and X activity levels. Initial target ranges for factor II and X were empirically set at 0.2–0.3 IU/mL (20–30%). On transfer day 53, factor II and factor X levels of 0.13 IU/mL (normal 0.5–1.50) and 0.09 IU/mL, respectively, were reported and the lepirudin infusion was discontinued. The patient was discharged on warfarin 7.5 mg/day and has maintained adequate anticoagulation with measurement of factor X levels between 0.10 and 0.35 IU/mL and factor II between 0.19 and 0.46 IU/mL over the subsequent 7 months (Table 2, Figure 1). Corresponding INR values during this period ranged from 2.8 to 5.88. Repeat DRVVTs 2 and 8 weeks after discharge confirmed the presence of a lupus anticoagulant (ratios >1.2 on both instances). The antiphospholipid antibody levels were still markedly elevated 8 weeks after discharge. D-Dimer levels did not significantly change from those at discharge.

**Table 2.** Outpatient Monitoring Profile

| Day[a] | Warfarin (mg/day) | INR | Factor X[b] (IU/mL) | Factor II[b] (IU/mL) | Comment |
|---|---|---|---|---|---|
| 3 | 7.5 | 2.69 | | 0.35 | |
| 7 | 7.5 | 2.80 | | 0.36 | |
| 15 | 7.5 | 4.90 | | 0.30 | |
| 24 | 7.5 | 5.19 | 0.13 | 0.25 | Bactrim |
| 31 | 4.0 | 3.54 | 0.19 | 0.30 | Bactrim stopped |
| 41 | 7.5 | 5.34 | 0.12 | 0.23 | |
| 43 | 7.5 | 4.81 | | | |
| 47 | 7.5 | 3.71 | | | |
| 55 | 7.5 | 4.95 | 0.10 | 0.22 | |
| 82 | 7.5 | 5.8 | 0.11 | 0.19 | |
| 110 | 7.5 | 5.88 | 0.10 | 0.20 | |
| 136 | 7.5 | 3.79 | 0.13 | 0.22 | |
| 162 | 7.5 | 2.75 | 0.17 | 0.30 | |
| 190 | 7.5 | 2.89 | 0.35 | 0.46 | |
| 204 | 10 mg (1 dose) 7.5 mg (6 doses) | 3.26 | 0.24 | 0.46 | |

INR = international normalized ratio.
[a]After hospital discharge.
[b]0.1 IU/mL = 10%.

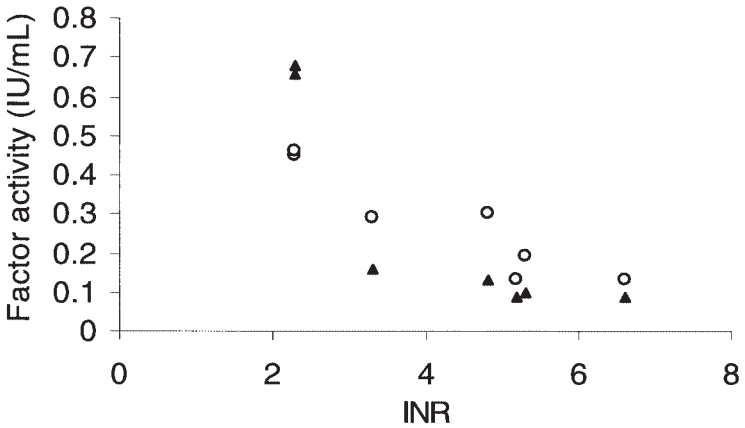


**Figure 1.** Relationship between international normalized ratio (INR) and factor II (❍) and X (▲) activities in a patient with a strong lupus anticoagulant undergoing warfarin therapy.

## Discussion

Antiphospholipid antibody syndrome (APS) and HIT are acquired immune disorders diagnosed by clinical presentation with positive laboratory assays.[3] The immune-mediated form of HIT is typically characterized by reduction in platelet count within 5–10 days after exposure to heparin and is associated with a high rate of thrombosis.[4] Approximately 2–4% of all patients receiving UFH develop HIT.[5] Although rare, HIT has also occurred with the use of LMWH.[6] Thrombocytopenia developing <5 days after heparin exposure can occur if a patient has been exposed to heparin within the past 100 days. Our patient received enoxaparin 2 months prior to transfer and developed thrombocytopenia after only 2 days of heparin exposure. Laboratory assays, such as platelet activation or functional assays, are useful adjuncts in distinguishing HIT-related thrombocytopenia from other causes.[7]

The current drugs used to manage HIT are DTIs such as lepirudin or argatroban or, in some cases, the heparinoid danaparoid. This is followed by conservative initial warfarin doses to avoid venous limb gangrene.[2] There is some evidence that DTIs bias coagulation assays.[8] Therefore, a pre-DTI treatment INR should be compared with a during-DTI treatment INR to determine the DTI effect, if any, on the INR. At our institution, we previously added therapeutic concentrations of lepirudin (2–3 times baseline aPTT; ~50–80 sec) to normal pooled plasma and demonstrated no significant change to INR values.[9] Therefore, we concluded that the elevated INR in this patient was not due to DTI therapy.

The etiology and mechanisms of APS are yet to be fully understood. Antiphospholipid antibodies are a heterogeneous group of autoantibodies not directed against phospholipids, but against proteins having bound phospholipids, as well as protein-phospholipid complexes formed with $\beta_2$-glycoprotein I, a plasma protein with anticoagulant properties.[10,11] Thrombosis in these patients has been speculated to occur via several potential mechanisms including the activation of endothelial cells and expression of tissue factor, oxidant-mediated injury of vascular endothelium, and modulation of phospholipid-binding proteins involved in the regulation of

the coagulation cascade.[12,13] The diagnosis of APS requires clinical (thrombosis) and laboratory evidence. The laboratory evidence includes tests for the presence of lupus anticoagulants and/or $\beta_2$-glycoprotein–dependent anticardiolipin antibody assays.[3]

Lupus anticoagulants have historically been detected by prolongation of the aPTT in patients without evidence of bleeding, heparin contamination, or factor deficiency. The paradox is that the prolongation of the aPTT due to lupus anticoagulants is associated with thrombosis. The mechanism of in vitro prolongation of the aPTT (and/or prothrombin time) is through the binding of the phospholipid present in the testing reagent by the antibodies present in the patients' plasma, resulting in prolongation of the clotting time. Several reports suggest variable sensitivity of laboratory reagents to the presence of lupus anticoagulants, which are dependent on the type and concentration of phospholipid used.[14-16] At our institution, we deliberately selected our aPTT reagent (Actin FS, Dade Behring) to be lupus anticoagulant insensitive, while our prothrombin time reagent (Innovin, Dade Behring) is sensitive to the presence of high-titer phospholipid antibodies.[17,18] This prolongation of our patient's INR in the absence of warfarin is highly suggestive of a phospholipid antibody effect, as other inhibitors that affect the INR are extremely rare. We also tested this patient's INR using a finger-stick method, which has less sensitivity to phospholipid antibodies, although there was no significant difference between the laboratory result and finger-stick result.

To confirm lupus anticoagulants, a phospholipid-dependent test is required.[19] We use a DRVVT and re-analyze any prolonged results of the test with a confirmation method that neutralizes the lupus anticoagulant effect. In this patient, we demonstrated a prolonged DRVVT, but the confirmation test on the patient sample demonstrated partial neutralization. We also demonstrated that the addition of a DTI to normal plasma will prolong the DRVVT and yield inconclusive neutralization testing. Therefore, during the lepirudin treatment course, we were unable to absolutely ascertain that the prolongation of the INR was due to a phospholipid antibody.

A relatively common finding in patients with lupus anticoagulants is prothrombinemia (decreased factor II levels) due to an autoantibody to factor II.[20] These antibodies are nonneutralizing and cannot be detected by traditional mixing studies with normal plasma. In our patient, it was unclear whether the frank prothrombinemia (factor II 0.07 IU/mL) was secondary to an autoantibody or just a delayed recovery from vitamin K replacement, especially since the patient later demonstrated normal prothrombin concentrations.

The development of high-titer phospholipid antibodies in this patient complicated her management, since an elevated INR was present in the absence of other causes such as liver disease or drug therapy. This interference made it difficult to determine whether the patient was being appropriately anticoagulated while on warfarin. Therefore, the challenge was how to monitor her anticoagulation after reinitiating warfarin, as some thromboplastins may be influenced in the presence of high titers of antiphospholipid antibodies. In these instances, adjustments of the target INR may be higher, up to 2.5–3.5. In the presence of high- titer inhibitors, rendering the INR unusable, alternative approaches to monitoring the anticoagulation effect of warfarin are necessary. An alternative approach was to follow clotting factor activity.

There are 2 primary means of determining levels of vitamin K–dependent clotting factor activity. A chromogenic method uses a reagent substrate that is labeled with a chromophore, so that when the reagent is bound to the target protein, a color is produced that is measured spectrophotometrically. A clot-based assay uses a modified prothrombin time or aPTT method. The postulated advantage of the chromogenic method is that no phospholipid membrane surface is required, and thus the method may not be influenced by the inhibitory effect of high-titer antiphospholipid antibodies. In patients with lupus anticoagulants, one study correlated a factor X reduction of 0.20–0.40 IU/mL to INR values between 2 and 3 using a chromogenic assay. Observed factor II activities were slightly lower than those of factor X.[21]

Clot-based, also termed amidolytic methods, may be used for factor assays even though the lupus anticoagulant prolongs the patient's prothrombin time and/or aPTT. In performing factor assays, the patient's plasma is usually diluted with a buffered saline solution prior to analysis. This dilution of the plasma will also dilute the high-titer antiphospholipid antibody effect, enabling the prothrombin time and/or aPTT reagent to be used for factor activity analysis. Reproducible results between serial dilutions and tests for parallelism between patient results and the test standard are procedural checks to determine whether there exists an inhibitor effect when performing factor activity assays. In our patient, the sample diluting effectively neutralized the inhibitory effect of the high-titer antiphospholipid antibodies, and we were able to accurately determine factor activity levels. One study reported factor X levels in the presence of lupus anticoagulant using an amidolytic factor X assay ranging from 0.20 to 0.30 IU/mL for INRs of 2–3 and from 0.11 to 0.20 IU/mL for INRs of 3–5.[22]

Although we were able to use amidolytic methods to measure factor activity levels in our patient, further challenges included using these data to manage anticoagulation. The data on factor activity levels and their correlation with INR values in patients receiving oral vitamin K antagonists is limited. No clear guidelines or published experience is available on initiating and adjusting warfarin dosing using clotting factor levels. One report suggested that factor II levels of 0.20–0.40 IU/mL correlated with an INR equivalent of 2–3.[23] D'Angelo et al.[24] expanded on this theory suggesting that prothrombin activation, instead of INR, had better correlation with factor II levels. Their research showed mean INR values of 2.9 (2.62–3.20) correlated with mean factor II levels of 0.30 IU/mL (0.27–0.34 IU/mL) and factor X levels of 0.11 IU/mL (0.09–0.13 IU/mL). However, others have observed that factor II levels measured during warfarin therapy may not correlate with measured therapeutic INR results, and a multivariate analy-

sis showed factor II levels to be the least significant of the 3 factors measured in determining the INR.[25-27] Looking at combined clotting factor levels appeared to be the best option for monitoring anticoagulation in our patient. In fact, Lind et al.[27] reported that the correlation of the INR was higher between the measurement of combined factors X and II (r = 0.72) than with factors X and VII (r = 0.37).

Since clotting factors reflected in the INR have variable elimination half-lives ($t_{1/2}$), the shortest, factor VII ($t_{1/2}$ 2–5 h), would indicate initial responses to warfarin. In our patient, we opted to use the factor VII activity measurement after the first 24 hours of warfarin therapy to determine the initial response to warfarin anticoagulation. The other vitamin K–dependent factors (factor X $t_{1/2}$ 20–42 h, factor II $t_{1/2}$ 48–120 h) have longer half-lives and therefore would be used to monitor long-term stabilized warfarin therapy.[28] We adjusted the warfarin dose to maintain factor X values subjectively at lower target values than previously observed (0.15–0.25 IU/mL) out of concern for the patient's hypercoagulable state. The factor II activities were concurrently measured and were slightly higher (0.19–0.30 IU/mL) than corresponding factor X activity levels. After 7 months of warfarin therapy, there has been no overt evidence of thrombosis or adverse events.

## Summary

Antiphospholipid antibodies (specifically lupus anticoagulant) have been shown to artificially prolong the clotting times of prothrombin time and aPTT tests, making these assays unreliable for monitoring anticoagulation. In our patient, consistently elevated INR values due to presence of high-titer antiphospholipid antibodies made warfarin monitoring challenging. Long-term warfarin therapy was accomplished by following the initial reduction of factor VII activity and then monitoring long-term anticoagulation with factor II and X activity levels.

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## References

1. Moll S, Ortel TL. Monitoring warfarin therapy inpatients with lupus anticoagulants. Ann Intern Med 1997;127:177-85.
2. Smythe MA, Warkentin TE, Stephens JL, Zakalik D, Mattsow JC. Venous limb gangrene during overlapping therapy with warfarin and a direct thrombin inhibitor for immune and heparin-induced thrombocytopenia. Am J Hematol 2002;71:50-2.
3. Levine JS, Branch W, Rauch J. The antiphospholipid syndrome. N Engl J Med 2002;346:752-63.
4. Fabris F, Ahmad S, Cella G, Jeske WP, Walenga JM, Fareed J. Pathophysiology of heparin-induced thrombocytopenia: clinical diagnosis and implications—a review. Arch Pathol Lab Med 2000;124:1657-66.
5. Walenga JM, Jeske WP, Messmore HL. Mechanism of venous and arterial thrombosis in heparin-induced thrombocytopenia. J Thromb Thrombolysis 2001;10(suppl):S13-20.
6. Warkentin TE, Levine MN, Hirsh J, Horsewood P, Roberts RS, Gent M, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. N Engl J Med 1995; 332:1330-5.
7. Warkentin T. Laboratory testing for heparin-induced thrombocytopenia. J Thromb Thrombolysis 2001;10(suppl):S35-45.
8. Hursting MJ, Zehnder JL, Joffrion JL, Becker JC, Knappenberger GD, Schwarz RP. The international normalized ratio during concurrent warfarin and argatroban anticoagulation: differential contributions of each agent and effects of the choice of thromboplastin used. Clin Chem 1999;45:409-12.
9. Dager WE, White RH. Authors' reply: treatment of heparin-induced thrombocytopenia (letter). Ann Pharmacother 2002;36:1484. DOI 10.1345/aph.1A204b
10. McNeil HP, Simpson RJ, Chesterman CN, Krilis SA. Anti-phospholipid antibodies are directed against a complex antigen that includes a lipid-binding inhibitor of coagulation: beta 2-glycoprotein I (apolipoprotein H). Proc Natl Acad Sci U S A 1990;87:4120-4.
11. Pengo V, Biasiolo A, Brocco T, Tonetto S, Ruffatti A. Autoantibodies to phospholipid-binding plasma proteins in patients with thrombosis and phospholipid-reactive antibodies. Thromb Haemost 1996;75:721-4.
12. Amengual O, Atsumi T, Khamashata MA, Hughes G. The role of tissue factor pathway in the hypercoagulable state in patients with antiphospholipid syndrome. Thromb Haemost 1998;79:276-81.
13. Walenga JM, Michal K, Hoppensteadt D, Wood JJ, Robinson JA, Bick RL. Vascular damage correlates between heparin-induced thrombocytopenia and the antiphospholipid syndrome. Clin Appl Thromb Hemost 1999;5(suppl 1):S76-84.
14. Denis-Magdeline A, Flahault A, Verdy E. Sensitivity of sixteen aPTT reagents for the presence of lupus anticoagulants. Haemostasis 1995;25: 98-105.
15. Adcock DM, Marlar RA. Activated partial thromboplastin time reagent sensitivity to the presence of the lupus anticoagulant. Arch Pathol Lab Med 1992;116:837-40.
16. Brandt JT, Triplett DA, Musgrave K, Orr C. The sensitivity of different coagulation reagents to the presence of the lupus anticoagulants. Arch Pathol Lab Med 1987;111:120-4.
17. Arnout J, Meijer P, Vermylen J. Lupus anticoagulant testing in Europe: an analysis of results from the first European concerted action on thrombophilia (ECAT) survey using plasmas spiked with monoclonal antibodies against human $\beta_2$-glycoprotein I. Thromb Haemost 1999;81:929-34.
18. Robert A, Le Querrec A, Delahousse B, Caron C, Houbouyan L, Boutirere B, et al. Control of oral anticoagulation in patients with the antiphospholipid syndrome—influence of the lupus anticoagulant on the international normalized ratio. Groupe Methodolgie en Hemostsae du Groupe d'Etudes sur l'Hemostasis et la Thrombose. Thromb Haemost 1998;80:99-103.
19. Arnout J. Antiphospholipid syndrome: diagnostic aspects of lupus anticoagulants. Thromb Haemost 2001;86:83-91.
20. Bajaj SP, Rapaport SI, Fierer DS, Herbst KD, Schwartz DB. A mechanism for the hypoprothrombinemia of the acquired hypoprothrombinemia–lupus anticoagulant syndrome. Blood 1983;61:684-92.
21. Moll S, Ortel T. Monitoring warfarin therapy in patients with lupus anticoagulants. Ann Intern Med 1997;127:177-85.
22. Bijsterveld NR, Middeldorp S, Berends F, Buller HR. Monitoring therapy with vitamin K antagonists in patients with lupus anticoagulant: effect on different tests for INR determination. J Thromb Thrombolysis 2000;9: 263-9.
23. Le DT, Weibert RT, Sevilla BK, Donnelly KJ, Rapaport SI. The international normalized ratio (INR) for monitoring warfarin therapy: reliability and relationship to other monitoring methods. Ann Intern Med 1994; 120:552-8.

24. D'Angelo A, Valle PD, Crippa L, Fattorini A, Pattarini E, D'Angelo SV. Relationship between international normalized ratio values, vitamin K–dependent clotting factor levels and in vivo prothrombin activation during the early and steady phases of oral anticoagulation treatment. Haematologica 2002;87:1074-80.
25. Paul B, Oxley A, Bringham K, Cox T, Hamilton PJ. Factors II, VII, IX and X concentrations in patients receiving long term warfarin. J Clin Pathol 1987;40:94-8.
26. Kumar S, Haigh JRM, Tate G, Bouthby M, Joanes DN, Davies JA, et al. Effect of warfarin on plasma concentrations of vitamin K dependent coagulation factors in patients with stable control monitored compliance. Br J Haematol 1990;74:82-5.
27. Lind SE, Callas PW, Golden EA, Joyner KA, Ortel TL. Plasma levels of factors II, VII, and X and their relationship to the international normalized ratio during chronic warfarin therapy. Blood Coag Fibrin 1997;8: 48-53.
28. Wittkowski AK. Thrombosis. In: Koda-Kimble MA, Young LY, eds. Applied therapeutics: the clinical use of drugs. 7th ed. Philadelphia: Lippincott Williams and Wilkins, 2001:14-5.

EXTRACTO

**OBJETIVO**: Informar sobre un caso de una paciente con el síndrome de anticuerpos a antifosfolípidos y trombosis múltiples que desarrolló trombocitopenia inducida por heparina (HIT) y, subsiguientemente, prolongación de la razón internacional normalizada (INR), posiblemente debido a los anticuerpos a antifosfolípidos. Se midió la actividad de los factores de coagulación II y X para ajustar la terapia a largo lazo de warfarina sin evidencia de complicaciones al completar 7 meses.

**RESUMEN DEL CASO**: Una mujer de 56 años de edad con historial de síndrome de anticuerpos a antifosfolípidos y trombosis en terapia crónica con warfarina fue ingresada al hospital por problemas gastrointestinales y se encontró con una INR >14. Se descontinuó la warfarina, se administró vitamina K, y se inició una infusión de heparina. Luego de 2 días, la paciente desarrolló trombocitopenia, hipotensión, taquicardia, hiponatremia, y dolor abdominal progresivo. Luego de transferirla a un centro de cuidado terciario, se le diagnostica HIT y se inicia una infusión de lepirudina. Subsiguientemente, ocurre una elevación súbita de la INR (>14) con una actividad de protrombina (factor II) baja. Cuando los valores de la INR bajaron a 2–3, se recomenzó la warfarina y se ajustó la dosis utilizando los niveles de actividad de factor X y II.

**DISCUSIÓN**: Típicamente se usa la INR para evaluar la intensidad de anticoagulación. El valor de INR representa la reducción de los factores II, VII, y X. En raras circunstancias, un inhibidor independiente o sustancia puede interferir con el proceso de medir la INR. En estas situaciones, un manejo alterno puede ser la medida directa de las concentraciones de los factores.

**CONCLUSIONES**: Los niveles de actividad de los factores II y/o X proveen un medio alterno para medir los efectos anticoagulantes de warfarina en presencia de un inhibidor significativo (anticuerpos a antifosfolípidos) que puede influenciar en la medida de la INR.

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RÉSUMÉ

**OBJECTIF**: Rapporter un cas de syndrome antiphospholipide ayant développé une thrombocytopénie à l'héparine (TIH) nécessitant une anticoagulation à base de warfarine. Le monitoring de ce patient étant rendu difficile par une prolongation du RNI secondaire aux anticorps, le suivi a été fait avec succès pendant 7 mois à l'aide de l'activité anti-IIa et anti-Xa.

**RÉSUMÉ**: Une patiente de 56 ans présentant un syndrome antiphospholipide sous warfarine pour prévenir des évènements thrombotiques, est admise pour des raisons gastro-intestinales. Un RNI de 14 étant mesuré, la warfarine est arrêtée, renversée avec de la vitamine K, et une perfusion d'héparine est débutée. À l'intérieur de 2 jours, une thrombocytopénie se développe, associée à de l'hypotension, de la tachycardie, une hyponatrémie, et des douleurs abdominales. Une TIH est diagnostiquée et la de lépirudine est débutée. Une brusque élévation du RNI (plus de 14) associée à une faible activité de la prothrombine est notée. La warfarine a été ré-instituée en ajustant les doses selon l'activité anti-Xa et anti-IIa.

**DISCUSSION**: Le RNI est utilisé pour suivre l'intensité de l'anticoagulation. Cette valeur représente l'activité des facteurs II, VII, et X. Dans de rares circonstances, une substance peut interférer avec les mesures, ce qui peut être évité en mesurant directement l'activité des facteurs de coagulation.

**CONCLUSIONS**: L'activité anti-Xa ou anti-IIa est une alternative valable pour mesurer l'intensité de l'effet anticoagulant de la warfarine chez des patients présentant des inhibiteurs circulants, comme des anticorps antiphospholipides.

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