Case Report

Monitoring Oral Anticoagulation May Require Determination of Single Coagulation Factor Activities in Patients with Antiphospholipid Syndrome

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ABSTRACT. We describe a 32-year-old man with secondary antiphospholipid syndrome (APS) who received oral anticoagulation with phenprocoumon after deep vein thrombosis. Conventional monitoring of oral anti-coagulation by INR measurement was impaired by coagulation factor inhibition *in vitro* due to a strong lupus anticoagulant. The case illustrates that monitoring of oral anticoagulation may require determination of single coagulation factor activities in selected patients with APS. (First Release Aug 1 2006; J Rheumatol 2006;33:1881–2)

Key Indexing Terms:
ANTIPHOSPHOLIPID SYNDROME   LUPUS ANTICOAGULANT
ORAL ANTICOAGULATION   MONITORING

Patients with antiphospholipid syndrome (APS) have a high risk for recurrent thromboembolic complications and therefore often receive prophylactic longterm oral anticoagulation following the first thromboembolic event. In this setting, the monitoring of anticoagulation may be compromised by antibody related influences on routinely used assays. We describe a case illustrating this potential pitfall in monitoring of oral anticoagulation in such patients.

CASE REPORT

A 32-year-old male patient receiving oral anticoagulation with phenprocoumon (target INR 2–3) was referred to our unit because of significant differences between laboratory and self-determined (CoaguChek®, Roche, Mannheim, Germany) values of prothrombin time and INR. He had had systemic lupus erythematosus (SLE) for more than 11 years. Several courses of immunosuppression with prednisolone and/or azathioprine had been given for treatment of clinical flares as well as for suspected lupus nephritis. One year prior to referral, he developed deep vein thrombosis of the left thigh; subsequently APS was diagnosed, and treatment with phenprocoumon was initiated. Results of oral anticoagulation monitoring were confusing, with major differences between laboratory and self-determined values. As a consequence of continuously increasing INR, the weekly phenprocoumon dosage was reduced from 7.5 mg to 3 mg to achieve an INR within the therapeutic range.

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Even though prothrombin time and INR suggested sufficient oral anticoagulation, our analyses including mixing studies with standard human plasma revealed unaffected coagulation activities of factors VII and X. By contrast, factor II and IX activities were significantly reduced in a 1:1 mixing study, which indicates strong inhibition through the presence of lupus anticoagulant (LAC) (Table 1). Because of these findings, conventional monitoring based on the determination of prothrombin time or INR was not useful. As a consequence, phenprocoumon dosage was adapted based on determination of factor VII and X activities, which were shown not to be influenced by LAC in this patient. Reference values for the therapeutic range of single clotting factor activities were obtained from 16 patients under phenprocoumon treatment with target INR 2–3. These patients were shown not to have LAC or other phenomena complicating adjustment of anticoagulation (Table 2). To yield therapeutic coagulation factor activities and thus sufficient anticoagulation, the phenprocoumon dosage had to be raised from 3 mg to 16.5 mg per week.

DISCUSSION

Antiphospholipid antibodies directed against proteins complexed with negatively charged phospholipids include anticardiolipin antibodies and LAC. These inhibitors can further be characterized by prolonging the clotting time of *in vitro* assays due to binding onto phospholipids in the test system.

Antiphospholipid antibodies are of clinical relevance since they predispose for recurrent venous thromboembolism, immune thrombocytopenia, and fetal loss[1]. This feature, termed APS, may occur primarily or in association with autoimmune disorders such as SLE[2].

In apparently healthy young control subjects, antiphospholipid antibodies are found with a prevalence of 1% to 5%[3]. Among patients with SLE, a significantly higher prevalence of cardiolipin antibodies (12%–30%) and LAC (15%–34%) has been reported[4]. About two-thirds of these patients develop APS with thromboembolic complications[3,5]. The high risk for thromboembolic complications underscores the need for longterm anticoagulation in this setting[6].

Table 1. Coagulation factor activities of the patient and results of mixture studies with standard human plasma (SHP). In contrast to factor VII and factor X, measured activities of factor II and IX, after mixing the patient's plasma with SHP (1:1), were lower than expected, indicating the influence of the lupus anticoagulant. Values are percentages.

Coagulation Factor	Patient Plasma	Standard Human Plasma	Mixing Study Expected	Measured	Result Positive	Negative
II	23	100	62	41	•	
VII	78	102	90	88		•
IX	9	91	50	31	•	
X	78	92	85	87		•

Table 2. Laboratory findings under conventional monitoring and following dosage correction of oral anticoagulation based on the determination of single coagulation factor activities.

	Monitoring Based on Prothrombin Time/INR	Monitoring Based on Factor VII and X Activities	Reference Values, ± SD*
Phenprocoumon dosage, mg/week	3	16.5	—**
Prothrombin time, %	39	23	30 ± 7
INR	2.2	3.2	2.5 ± 0.5
Factor II activity, %	23	10	33 ± 9
Factor VII activity, %	77	57	33 ± 11
Factor IX activity, %	9	9	65 ± 12
Factor X activity, %	78	21	18 ± 5

* Reference values obtained from laboratory data of 16 patients under anticoagulation with phenprocoumon.
** Data not shown because of interindividual variance.

However, monitoring of oral anticoagulation is a critical factor because of antibody-related influence on routine coagulation assays. In particular, LAC can lead to artificially low clotting factor activities and increased INR in a subgroup of about 6.5% of patients with APS[7]. These patients can be identified by failure to achieve adequate correction of prothrombin time with addition of normal plasma to their own plasma[7]. As a consequence of LAC-dependent falsely pathological coagulation assays, inadequately low dosage of oral anticoagulants may result and contribute to recurrent thromboembolism in these patients. This may also explain the finding that some of these patients are only efficiently protected against recurrent thromboembolism with a more intense oral anticoagulation, i.e., a target INR of 3.0 and 4.0 rather than 2.0 to 3.0[8]. In our case, sufficient anticoagulation was achieved by monitoring based on single coagulation factor activities and independent from prothrombin time or INR.

In patients with LAC the adjustment of oral anticoagulation by prothrombin time and INR can be impaired by determination of falsely low coagulation factor activities. Although the determination of INR is the standard procedure for monitoring oral anticoagulants, the INR can be misleading in some patients with APS. In these patients, monitoring anticoagulation by determining single coagulation factor activities not influenced by LAC is required. This approach may help to avoid inadequately low dosage of oral anticoagulants and to decrease the frequency of recurrent thromboembolism in this setting.

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