Thrombosis

Anticoagulation in the antiphospholipid syndrome

Our objectives were to evaluate thrombotic complications in patients with lupus anticoagulant fulfilling Sapporo criteria, anticoagulated with an intended INR 2.0-3.0 due to venous and arterial thrombosis. In our series standard anticoagulation was safe and efficacious in preventing recurrences in patients with systemic lupus erythematosus, with other thrombophilia and with arterial thrombosis.

haematologica 2004; 89:503-504
(*http://www.haematologica.org/journal/2004/4/503*)

Antiphospholipid syndrome (APS) is associated with a high risk of thrombosis recurrence.[1,2] Some authors have proposed that this risk justifies a higher intensity of anticoagulation than *normal*,[1] but this is not supported by recent data.[3-5] It has also been suggested that venous and arterial thromboses should be managed differently.[6]

Our objectives were to evaluate thrombotic complications in patients with APS who were being anticoagulated to maintain an intended international normalized ratio (INR) of 2.0-3.0. We focused on lupus anticoagulant (LA), since this is a stronger risk factor[7] than anticardiolipin antibodies (aCL), and tried to identify risk factors for recurrent thrombosis. The patients included in the study attended the Thrombosis Department at the National Academy of Medicine in Buenos Aires. The study was ambispective (retrospective: 1988-1998, prospective: 1999- 2002). Criteria for inclusion in the study were fulfillment of Sapporo's criteria[8] and chronic anticoagulation due to venous and/or arterial thrombosis with an intended INR of 2.0-3.0.

LA determinations were performed according to SSC-ISTH recommendations.[9] IgG and IgM aCL were tested by an ELISA assay (*The Binding Site Limited*). Screening for other causes of thrombophilia was performed in young patients and in those with idiopathic events. Embolic complications (defined as the presence of a new thrombotic event, regardless of the initial site) and recurrences (reappearance of thrombosis in the initial location), triggering events and predisposing factors were recorded. Only symptomatic patients underwent objective evaluation. Major bleeding was defined as in previous reports.[10]

Ninety-three anticoagulated patients with APS were positive for LA. Seventy-nine patients fulfilled the inclusion criteria for this study and none was lost from follow-up. The characteristics of these patients and their treatment are listed in Table 1. Twenty-six patients (33%) were followed-up ambispectively. The prospective phase included 45 patients (57%) while 8 (10%) were studied only retrospectively. The total follow-up was 259.16 years (median: 37.62±48.9 months) Patients spent 39.88 years (15.4% of the total follow-up) with an INR below the intended range and 65.92 years (25.5% of the time) with an INR above the intended range. Concomitant thrombophilic disorders were evaluated in 70/79 patients; the results are shown in Table 2. One 17 year-old girl with SLE and an ischemic stroke had an IgM titer at diagnosis of 112 MPL but this decreased to normal during the follow-up. Patients with both arterial and venous events were older (60.25 years ±17.02) than patients with thrombosis only in arterial (42.39 years ±17.17) or in venous sites (41.5 years ±12.25) (p=0.01). There were no differences in clinical presentation, in follow-up, or in outcome according to whether SLE was diagnosed.

There were no episodes of major bleeding except in one 27-year old SLE patient with LA who had a recurrent thrombotic event. This patient was anticoagulated because of two episodes of pulmonary embolism (PE) and had had an inferior caval vein filter (IVCF), Mobin-Udin, placed in 1986. In August 1987 she had a new PE while her INR was 2.1. She was set a higher INR range (3.0-3.5) and had no further complications. In 2003, LA was still positive. Evidence on the efficacy and safety of standard anticoagulation in APS is becoming available. The WAPS Study[4] showed no differences in thrombotic events between patients receiving high intensity or conventional anticoagulation treatment, but the population investigated was small and the median follow-up was short. A cumulative analysis of prospective trials reporting recurrent thrombosis in APS[5] showed no increased risk in patients with an INR between 2.0-3.0. The randomized, double-blind trial by Crowther[3] confirmed this finding although triggering events and additional risk factors were not analyzed. In our series of 79 patients, standard anticoagulation

Table 1. Patients' characteristics.

Numbers	*79*
Median age in years ±SD	44±16.95
(range)	(7-88)
Sex (n)	
Female	50
Male	29
SLE (%)	10 (12.7%)
Thrombotic events (%)	
venous	54 (68.4%)
arterial	17 (21.5%)
venous and arterial	8 (10.1%)
First idiopathic event	52
Recurrent event	27
(before anticoagulation)	
Concomitant thrombophilic conditions (%)	12 (15.1%)
Total follow up (years)	259.16
Prospective phase	56.9
Ambispective phase	181.7
Retrospective phase	20.56
Years with INR 2.0-2.9 (%)	153.36 (59.1 %)
Years below intended INR (%)	39.88 (15.4 %)
Years above intended INR (%)	65.92 (25.5 %)

Table 2. Concomitant prothrombotic disorders.

	Numbers
ACL	6 (1 medium titer and 1 high titer)
Hyperhomocysteinemia	6
Factor V Leiden	2
High PAI-1 levels or bad response to venous (10 minute) occlusion test	3
Congenital protein S deficiency	1

was effective in preventing recurrences in patients with SLE and in patients with other causes of thrombophilia. However, since information for combined thrombophilic states is lacking in the most recent communications,[3-5] further investigation is needed to assess whether combined thrombophilia requires different management.

A recent consensus meeting suggested that a target INR of 2.5 may not be enough to prevent recurrences in patients with stroke.[6] In our experience, arterial thrombosis did not behave differently from venous thrombosis. Moreover, patients with both arterial and venous thrombosis also remained free from recurrences during the follow-up despite being older. Our study, which included ambispective data and a long follow-up, adds to the observations by Crowther[3,5] and Finazzi[4] that standard anticoagulation is efficacious and safe, even in patients with concomitant prothrombotic conditions. Finally, we identified possible clinical predisposing factors for recurrence, having observed recurrent PE in a patient with two previous episodes and an IVCF. The number of previous events and the rheologic disturbance due to the filter are prognostic factors for recurrence. Patients with predisposing factors may need to be managed by setting a higher target INR.

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Funding: PC was funded by the Fundación René Barón.

Key words: oral anticoagulation, antiphospholipid syndrome, thrombosis recurrence.

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Thrombosis

Patient-specific errors in agreement between International Normalized Ratios measured by a whole blood coagulometer and by a routine plasma-based method

We applied a new statistical method[1] to improve comparisons between systems measuring prothrombin time (PT) by splitting disagreement into systematic errors, which can be eliminated, and random errors, which can not. We found that the disagreement between International Normalized Ratio (INR) measurements based on plasma and whole blood was significantly patient-dependent.

haematologica 2004; 89:504-505
(*http://www.haematologica.org/journal/2004/4/504*)

A number of studies have sought to investigate the accuracy[2] of whole blood coagulometers by comparison with plasma-based methods. Usually, however, only the systematic component of trueness (the mean difference) is evaluated whereas the other component, the random variation between patients, is neglected.

In cases in which the two PT systems to be compared are alike (e.g. if both are automatic and based on analysis of plasma with plain thromboplastin preparations) the random component may be small.

However, in other situations, as demonstrated in a recent study,[1] the random component may be large, indicating that the test system is unable to produce measurements that agree with the reference system across patients, even after appropriate calibration.

Our study included 64 consecutive patients on stable oral anticoagulation (OAT) who were seen for routine laboratory control of INR at Skejby Sygehus, Aarhus University Hospital. They had their INR measured by two types of portable whole blood coagulometers (CoaguChek (CC) and CoaguChek S (CCS), Roche Diagnostics, Mannheim, Germany) described elsewhere,[3] and a plasma based method routinely used in our central laboratory (LAB). The thromboplastin preparation used in the LAB was Nycotest (rabbit, combined, ISI approximately 1, manufactured by Axis-Shield PoC AS, Oslo, Norway) and the LAB PT system was calibrated on site by means of two plasma calibrators with assigned INR, provided by the Danish Institute of External Quality Control in Hospital Laboratories. Four CC devices were randomly selected and four CCS devices were supplied by the manufacturer. Each of the 32 combinations of CC, CCS, and order of device type was run in 2 patients, such that the total number of runs, randomized over patients, was 64 and the total number of CC and CCS measurements was 128. The same lot (no. 169) of test strips was used for all measurements on both the CC and CCS devices.

Figure 1 contains scatterplots of logarithmic INR values for CC, CCS and LAB. Ten patients had a LAB INR less than 1.1 and were excluded from further analysis. We found a systematic difference of 6.7% (95% confidence limits 4.6%,