Patients with antiphospholipid antibodies and venous thrombosis should receive long term anticoagulant treatment

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Abstract

Objective—To determine whether the finding of antiphospholipid antibodies in patients with venous thromboembolic episodes should influence the duration of treatment with anticoagulant drugs by mouth.

Methods—A retrospective study was carried out in 19 patients with antiphospholipid antibodies and a history of venous thromboembolic episodes. The median follow up from the first venous thromboembolic episode was 93 months and the median age at this episode was 26 years. The patients had in total 34 venous thromboembolic episodes. The total follow up period comprised 32 periods with and 23 periods without anticoagulant drugs.

Results—The probability of being free of recurrent venous thromboembolic episodes, calculated by the Kaplan-Meier method, was significantly influenced by the use of anticoagulant drugs. Patients receiving oral anticoagulants had at eight years a 100% probability of survival without recurrence, whereas patients in whom anticoagulant drugs were stopped had a 50% probability of a recurrent venous thromboembolic episode at two years, and a 78% probability of recurrence at eight years.

Conclusion—Patients with venous thromboembolic episodes and antiphospholipid antibodies have a high risk for recurrent venous thromboembolic episodes and long term treatment with anticoagulant drugs by mouth is an effective prophylaxis.

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vascular thrombosis six to 12 weeks after withdrawal of warfarin. These observations raise the question of whether patients with antiphospholipid antibodies should be treated with anticoagulant drugs for longer than the usual period of a few weeks to months after a venous thromboembolic episode. Owing to the limited number of eligible patients at each centre and the necessity for long term follow up, an answer to this question is not expected quickly from data of prospective randomised trials. Therefore we performed a careful retrospective analysis of the patients with antiphospholipid syndrome and venous thrombosis followed up at our institution.

Patients and methods

PATIENTS

In the total group of 96 patients with antiphospholipid antibodies (lupus anticoagulant or anticardiolipin antibodies, or both) who were known at our lupus clinic in February 1992 there were 19 patients (16 women) with a history of venous thromboembolic episodes. All had IgG class anticardiolipin antibodies; 9/19 patients were also positive for IgM class anticardiolipin antibodies and lupus anticoagulant. Lupus anticoagulant or IgM class anticardiolipin antibodies were present in 5/19 and 3/19 patients respectively. The median follow up from the first venous thromboembolic episode to February 1992 was 93 months (range 11–248 months). The median age at the first venous thromboembolic episode was 26 years (range 15–40 years). None of the patients was referred to us because of such episodes.

In February 1992 12/19 patients had systemic lupus erythematosus (SLE),⁵ 6/19 had lupus-like disease, and one had primary antiphospholipid syndrome.⁶ The table gives abnormalities in the patients with lupus-like disease.

We carefully reviewed the patients' records, focusing on thromboembolic episodes, risk factors for venous thromboembolic episodes, duration, intensity, and complications of treatment with anticoagulant drugs and on manifestations of SLE. For each venous thromboembolic episode the presence or absence of erythrocytosis or thrombocytosis, malignancy, oral contraceptives containing oestrogen, nephrotic syndrome, active SLE, immobilisation, and pregnancy was determined. Information was completed by an additional interview with the patient or the primary doctor, or both.

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Antiphospholipid antibodies are the serological hallmark of the antiphospholipid syndrome.¹ The major clinical manifestations of the antiphospholipid syndrome are venous and arterial thrombosis, recurrent fetal loss, and thrombocytopenia. From case reports there is the impression that patients positive for antiphospholipid antibodies have a high chance for recurrent thrombosis.² In patients with cerebral ischaemia this has been confirmed in a controlled study.³ Comparable data are not available for venous thrombosis. Asherson *et al*⁴ described six patients with antiphospholipid syndrome and recurrence of

Table 1 Abnormalities in six patients with lupus-like disease

Patient No	Clinical and serological abnormalities*
3	Nailfold lesions, arthritis, thrombocytopenia, Coombs+, ANA+, aDNA+, low complement
8	Tendinitis, ANA+, aSS-A+, aSS-B+
12	Atypical skin rashes, arthralgia, Raynaud's phenomenon, leucocytopenia and thrombocytopenia, ANA+
17	Polyarthritis, polytendinitis, ANA+
18	Discoid lupus erythematosus, photosensitivity
19	ANA+

*ANA+=positive test for antinuclear antibodies using Hep-2 cells as a substrate and a serum dilution of at least 1:400; aDNA+=positive for antibodies to DNA; aSS-A/aSS-B=positive for antibodies to SS-A/SS-B.

THROMBOEMBOLIC MANIFESTATIONS

Superficial thrombophlebitis was a clinical diagnosis. The presence of deep venous thrombosis was confirmed by venography, impedance plethysmography, or ultrasound. A diagnosis of pulmonary emboli included perfusion-ventilation mismatches at lung scanning; a diagnosis of portal vein thrombosis was based on angiographic findings.

LABORATORY TESTS

To determine the presence of lupus anticoagulant, three assays (activated partial thromboplastin time, phospholipid dilution test, and kaolin clotting time) were performed with platelet poor plasma as described previously.⁷ Lupus anticoagulant was considered present when at least two assays were positive. IgG and IgM anticardiolipin antibodies were measured with an enzyme linked immunosorbent assay (ELISA) as described previously.^{7, 8} Patients were regarded as positive for antiphospholipid antibodies when lupus anticoagulant or anticardiolipin antibodies, or both, were shown in at least two samples taken eight weeks apart.

Antithrombin III, antigen levels of protein C, protein S, and prothrombin were determined as described previously.⁹

STATISTICS

For the calculation of the probability of survival without thrombosis, the Kaplan-Meier method was used. Statistical significance was tested by the log rank test.

Results

The 19 patients had a total of 34 venous thromboembolic episodes (fig 1). The number of venous thromboembolic episodes was one in seven patients, two in nine patients, and three in another three patients. The venous thromboembolic episodes were thrombosis of the deep leg veins or pelvic veins, or both (19 events), extensive superficial thrombophlebitis (one event), pulmonary emboli (seven events), deep vein thrombosis complicated by pulmonary emboli (six events), and portal vein thrombosis (one event). The median follow up period from the first venous thromboembolic episode was 101 months (range 16–248 months) in 12 patients with recurrences, and

Figure 1 Follow up beginning at the time of the first venous thromboembolic episode up to February 1992 in 19 patients positive for antiphospholipid antibodies. Each triangle indicates a venous thromboembolic episode. Horizontal bars indicate treatment with anticoagulant drugs by mouth. A circle indicates an arterial thrombotic event.

28 months (range 11–101 months) in those with a single episode (seven patients).

During the follow up period arterial thrombosis occurred in three patients (thrombosis of the distal aorta in patient 1 and myocardial infarction in patients 3 and 4). In patients 3 and 4 myocardial infarction occurred during adequate treatment with oral anticoagulants (international normalised ratio at admission 3.6 and 2.6 respectively).

In all but one patient (patient 18) the follow up period could be divided into periods with and without treatment with oral anticoagulants. Treatment with anticoagulant drugs aimed at an international normalised ratio between 2.5 and 4.0. The 19 patients had a total of 32 periods with (one to three for each patient; median eight months, range 1.5–179 months) and 23 periods without (one to three for each patient; median nine months, range 1–101 months) use of anticoagulant drugs. The time relation between use of anticoagulant drugs and thrombotic episodes is shown in fig 1. Patients 6 and 8 were not treated with anticoagulant drugs after their initial thrombotic events, which were extensive superficial thrombophlebitis (patient 6) and portal vein thrombosis (patient 8).

Patient 1 had a recurrent venous thromboembolic episode while receiving oral anticoagulants (for 168 months). The international normalised ratio at admission was 2.2.

Eleven patients had at least one recurrence of a venous thromboembolic episode after a period in which no anticoagulant drugs were used (median period without anticoagulant

drugs between first and second thrombosis 5.5 months; range 1.25–88 months).

The probability of survival free from venous thromboembolic episodes with and without oral anticoagulants was calculated by Kaplan-Meier method (fig 2). There was a significant difference between the two groups (log rank test $p=0.000007$). Patients receiving anticoagulant drugs had a 100% probability of survival free from venous thromboembolic episodes at eight years. In contrast, the probability of recurrence of venous thromboembolic episodes when anticoagulant drugs were stopped was 50 and 78% at two and eight years respectively.

Two patients (patients 7 and 11) had a major bleeding complication while receiving anticoagulant drugs. Patient 7 was admitted with severe menorrhagia and a haemoglobin level of 39 g/l eight months after the start of treatment with oral anticoagulants. Patient 11 had intra-abdominal bleeding caused by an ovarian apoplexy when she was receiving anticoagulant drugs 32 months after her second venous thromboembolic episode. The two patients were treated with doses of anticoagulant drugs which were too high, as indicated by the values of the international normalised ratios at admission of 7.5 and 7.3.

All patients had normal levels of antithrombin III, protein C, and protein S. None had erythrocytosis, thrombocytosis, or a malignancy.

Oral contraceptives containing oestrogen were used at the time of 11/34 venous thromboembolic episodes in 10 patients. The ethinyloestradiol content of the birth control pills was 0.05 mg in two, 0.0375 mg in two, and 0.03 mg in seven episodes.

Active SLE (nephrotic syndrome in two, non-infectious fever in one patient) was present at the time of 3/17 venous thromboembolic episodes that occurred after a diagnosis of SLE was made. Two of these three venous thromboembolic episodes were also related to immobilisation. None of the other episodes was associated with immobilisation or an intercurrent illness.

Figure 2 Kaplan-Meier plot of probability of venous thromboembolic episode (VTE)-free survival calculated from 32 periods with oral anticoagulants (curve A) and 23 periods without anticoagulant drugs (curve B) in 19 patients positive for antiphospholipid antibodies. In February 1992 11 patients were receiving oral anticoagulants and eight patients were not. These patients are indicated in the figure by ticks on the curves. The curves differ significantly; $p=0.000007$ with log rank test).

A total of 4/34 venous thromboembolic episodes in four different patients were related to pregnancy. One occurred at a gestational age of 13 weeks; the other three were within the six week postpartum period.

In 17/34 venous thromboembolic episodes no additional risk factors could be found. In 10/12 patients with recurrent venous thromboembolic episodes, at least one episode occurred in the absence of additional risk factors.

Discussion

Our study shows that patients with a venous thromboembolic episode and antiphospholipid antibodies have an extremely high risk for recurrent venous thrombosis after withdrawal of treatment with oral anticoagulants. Most of the recurrences occur within the first year after the withdrawal of anticoagulant drugs, as indicated by a probability of venous thromboembolic episode-free survival at one year of 55% (fig 2). At eight years the probability of being free of recurrent venous thromboembolic episodes was 22%. Such a high frequency of recurrence is not found in unselected groups of patients with deep vein thrombosis,¹⁰ but is well known in patients with a persistent risk factor such as inherited deficiency of antithrombin III, protein C, or protein S.¹¹

The data show that treatment with oral anticoagulants at an international normalised ratio level between 2.5 and 4.0 is effective in preventing the recurrence of venous thrombosis in patients with antiphospholipid antibodies. The only venous thromboembolic episodes that occurred during treatment with oral anticoagulants (for 14 years) was during inadequate anticoagulation, as indicated by an international normalised ratio of 2.2. Our results are similar to those from a retrospective study of antithrombotic treatment in 70 patients with antiphospholipid antibodies and arterial or venous thromboembolic events.¹² That study concluded that recurrent thrombosis is a potentially serious problem for patients with antiphospholipid antibodies and that warfarin prophylaxis with an international normalised ratio greater than 2.6 is effective. These observations also correspond to those from Asherson *et al*,¹³ who considered inadequate treatment with warfarin (international normalised ratio between 2 and 2.5) to be responsible for recurrent thrombotic events in 4/9 patients with antiphospholipid syndrome in a five year follow up study.

Long term treatment with oral anticoagulants given at a high therapeutic level is not without risks, as is illustrated by the two serious bleeding complications we encountered in 19 patients. In our opinion this risk should be taken, given the high risk of potentially fatal venous thromboembolic episodes in these young patients. From our study it cannot be excluded that less intense treatment with anticoagulant drugs might also be effective, but other data^{12 13} suggest that anticoagulation at an international normalised ratio less than 2.0 is an inadequate prophylaxis for these patients.

From this study we conclude that continuation of treatment with oral anticoagulants is indicated in patients who have had a venous thrombosis and in whom antiphospholipid antibodies are repeatedly found. Although our study has the drawback of being retrospective, we changed our policy completely once these data were available. We feel that awaiting the results of prospective randomised trials would leave an important risk group unprotected for an unacceptable period of time. Prospective studies to define precisely the rate of occurrence of repeated thrombosis in unselected patients are urgently needed, however, to determine whether our treatment strategy can be generalised.

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