MATTERS ARISING

Long term anticoagulant treatment in the antiphospholipid syndrome

The interesting paper recently published by Derksen *et al* in the *Annals*[1] on the need for a long term anticoagulant treatment in patients with antiphospholipid antibodies and venous thrombosis prompts several observations.

(a) Four of the 19 patients had venous thromboembolic episodes during pregnancy or in the immediate postpartum period. To make their conclusion more valid, could the authors specify if pregnancy-associated events were initial or recurrent thrombosis? Oral anticoagulants cannot be used at that time, where the risk of thrombosis is obviously high, so pregnancy-associated thrombosis should probably be excluded from analysis. This also applies to the study by Rosove *et al*, which included three subsequent thromboses occurring during pregnancy or post-partum.[2]

(b) An oestrogen containing pill was used by 10 of the 19 patients at the time of 11/34 venous thromboembolic episodes. It is not clear if the pill was stopped after the initial episode, as recommended by most authors.[3] If it was not, the risk of recurrent thrombosis was overestimated in patients still receiving the pill.

(c) For clinicians, the problem is to avoid recurrent thrombotic events, irrespective of their site, venous or arterial. In the study by Derksen *et al*, myocardial infarction occurred in two patients despite 'adequate' anticoagulation, which demonstrates that the vascular protection provided by anticoagulants is not absolute.

(d) During the past years, growing evidence has emerged favouring the long or even very long term use of anticoagulants in patients with antiphospholipid syndrome. A major problem is to determine the duration of this treatment, since it is recognised as carrying a serious risk especially at an international normalised ratio of three or more.[1 2] It is assumed that anticoagulants are required as long as antiphospholipid antibodies are present.[2] To test the validity of this recommendation, could Derksen *et al* mention the sequential determinations of antiphospholipid antibodies in their patients, with and without relapses?

At present, the prevention of recurrent thrombotic events in the antiphospholipid syndrome is still a matter of debate. Two retrospective studies favour the use of oral anticoagulants.[1 2] Conversely, antiplatelet agents have been said to be effective in patients with focal cerebral ischaemia and antiphospholipid antibodies.[4] Prompt relapses may occur after warfarin[5] or aspirin[6] withdrawal. A clear and definitive answer, if any, requires prospective controlled trials such as the recently undertaken French cooperative study comparing aspirin to warfarin (AWAPS).

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1 Derksen R H W M, de Groot P G, Kater L, Nieuwenhuis H K. Patients with antiphospholipid antibodies and venous thrombosis should receive long term anticoagulant treatment. *Ann Rheum Dis* 1993; **52:** 689–92.
2 Rosove M H, Brewer P M C. Antiphospholipid thrombosis: clinical course after the first thrombotic event in 70 patients. *Ann Intern Med* 1992: **117:** 303–8.
3 Asherson R A. Antiphospholipid antibodies and syndromes. In: Lahita R G, ed. *Systemic lupus erythematsus.* New York: Churchill Livingstone, 1992: 587–635.
4 Levine S R, Brey R L, Joseph C L M, *et al.* Risk of recurrent thromboembolic events in patients with focal cerebral ischemia and antiphospholipid antibodies. *Stroke* 1992; **23** (suppl 1): 1/29–1/32.
5 Asherson R A, Baguley E, Pal C, Hughes G R V. Antiphospholipid syndrome: five year follow up. *Ann Rheum Dis* 1991; **50:** 805–10.
6 Le Thi Huong Du, Wechsler B, Edelman P, *et al.* Postpartum cerebral infarction associated with aspirin withdrawal in the antiphospholipid antibody syndrome. *J Rheumatol* 1993; **20:** 1229–32.

AUTHORS' REPLY: We read with great interest the letter from Drs Piette and Wechsler concerning our recent paper in the *Annals* on anticoagulant treatment in patients with antiphospholipid antibodies and venous thrombosis.[1] We wish to make the following comments:

1) In our series four thrombotic episodes were pregnancy related. These were initial thrombosis in two patients (numbers 5 and 12) and a recurrent thrombosis in patient number 6 and 10. In 10 patients low-dose oestrogen containing pills were used at the time of the first episode. These pills were stopped in all but one (number 17). Our data are insufficient to answer the question whether patients with antiphospholipid antibodies are more at risk for thrombosis in the presence of other risk factors (such as oestrogen-containing pills, pregnancy, immobilisation, cigarette smoking or hypercholesterolemia). However, our observation that additional risk factors were absent in 17/34 venous thromboses and in at least one of the episodes in 10/12 patients with recurrent thrombosis indicates that antiphospholipid antibodies itself are a risk factor, and argues against the universal need for a 'second hit' for thrombosis to occur.

2) Myocardial infarction that occurred in two patients during treatment with oral anticoagulants suggests that this therapy does not prevent arterial thrombosis in all patients. In both patients we added low-dose aspirin to treatment with oral anticoagulants.

3) Our patients were re-tested at least every six months and all but one remained positive. The exception was patient number 4. He became negative for antiphospholipid antibodies six months before myocardial infarction and is still negative two years later. This suggests that disappearance of antiphospholipid antibodies (defined as lupus anticoagulants and anticardiolipin antibodies) does not imply disappearance of the risk for thrombosis, and agrees with data showing that antibodies causing positive tests for antiphospholipid antibodies may differ from those causing thrombosis.[2]

We agree that the optimal therapy for patients with the antiphospholipid syndrome still has to be established. All clinical data that have been previously reported may suffer from selection bias. We need data from prospective trials on unselected patients and adequate control groups. Such trials should stratify for any other underlying disease, type and titre of antiphospholipid antibodies, other risk factors for thrombosis, and type of initial event. Due to the large number of patients required and the expected rate of (re-)thrombosis they should be multicentre and have many years of follow up. Such treatment trials are complex, expensive and in the end probably easy to combat. Furthermore, in each trial only a limited number of the many possible strategies for prophylactic treatment in patients with the antiphospholipid syndrome can be tested.

We very much applaud the initiatives taken by our French colleagues collaborating in AWAPS and hope that their study will result in a safe and effective therapy of patients with antiphospholipid syndrome. In the meantime, we advise long-term treatment with oral anticoagulants in all patients with antiphospholipid antibodies and venous thrombosis because these patients have a very high risk of recurrent venous thrombosis, and oral anticoagulants in contrast to acetyl salicylic acid, effectively prevent the recurrence of venous thrombosis.

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1 Derksen R H W M, de Groot Ph G, Kater L, Nieuwenhuis H K. Patients with antiphospholipid antibodies and venous thrombosis should receive long term anticoagulant treatment. *Ann Rheum Dis* 1993; **52:** 689–92.
2 Oosting J D, Derksen R H W M, Bobbink I W G, Hackeng T M, Bouma B N, de Groot Ph G. Antiphospholipid antibodies directed against a combination of phospholipids with prothrombin, protein C, or protein S: an explanation for their pathogenic mechanism? *Blood* 1993; **81:** 2618–25.

Evaluating new physical treatments

I am grateful for the opportunity to respond to your Leader article *Evaluating new physical treatments.*[1]

Let me start by describing myself as one of the author's electrotherapy "cynics", being extremely sceptical of claims made for these modalities and rarely use them. However, as this is a controversial area of research, results are required from a series of well designed, controlled trials, such as the excellent study by Heussler *et al*,[2] so that a measured judgement on the efficacy of the treatment can be taken. Pre-empting these studies and making inferences from results of a single study would be unscientific. Moreover, electrotherapy modalities are usually performed as an adjunct to treatments that aim to increase strength and range of movement, and here their production of "analgesia through a powerful placebo effect"[2] may be extremely useful.

It is somewhat strange that the author readily advocates massage by manipulators and nurses, even though massage is poorly evaluated. Furthermore, citation of the trial claiming chiropractic was superior to physiotherapy in the treatment of low back pain,[3] demonstrates the danger of attaching too great a significance to results of isolated trials. Critical assessment of the chiropractic study's design, execution and data analysis suggests it was seriously flawed, and its exaggerated and misleading conclusions have been widely challenged.[4–6] It therefore seems unwise for the author to suggest NHS