Optimizing the duration of anticoagulation therapy for venous thrombosis

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Clinical research on venous thromboembolism has helped to optimize the diagnosis and management of deep vein thrombosis and pulmonary embolism. Clear concepts are emerging with respect to how best to provide initial therapy with unfractionated, or low-molecular-weight, heparin. A number of studies have also attempted to establish the optimal duration of anticoagulation therapy in patients without concurrent malignant disease. In determining the length of treatment, the risk of thromboembolism recurring once the anticoagulant therapy is stopped must be weighed against the risk of bleeding if the therapy is continued. Although there are no definitive guidelines that apply to all patients, emerging evidence suggests that the risk of recurrent thromboembolism is sufficiently high in some patient groups to favour extended anticoagulation therapy. This high risk of recurrence is well known in patients with an underlying malignant disease. In patients without cancer, clinical variables that should be taken into account include a prior history of venous thromboembolism, transient or permanent clinical risk factors, and biochemical risk factors such as the factor V Leiden mutation.

Schulman and colleagues[1] undertook a prospective comparison of 6 weeks versus 6 months of oral anticoagulation therapy in patients who had experienced a first episode of venous thromboembolism and had no overt cancer; their results clearly favoured the longer treatment period. When temporary risk factors such as surgery, trauma, immobilization or estrogen therapy were present, recurrence rates in the next 24 months were 8.6% in the 6-week group and 4.8% in the 6-month group. Among patients without clinical risk factors, or who had idiopathic thrombosis, the recurrence rates were 24.2% versus 12.1% in the 2 treatment groups respectively. Thus, the longer therapy was more beneficial for all patient categories considered. Moreover, the rate of recurrent thrombosis even after 6 months of treatment was not insignificant among patients without clinical risk factors. This recurrence rate, although relatively lower than that reported by other researchers,[2] is in excess of the potential rate of bleeding complications among patients receiving long-term anticoagulation therapy[3] and raises the question of whether extended therapy might be beneficial for such patients.

Schulman and colleagues[4] concurrently conducted a prospective study in which patients who experienced a second episode of venous thromboembolism were randomly assigned to receive anticoagulation therapy for 6 months or for an indefinite period. After 4 years of follow-up, the rate of recurrent thromboembolism was only 2.6% among patients receiving prolonged treatment, versus 20.7% among those treated for 6 months. This pronounced benefit from extended treatment was tempered by a 8.6% incidence rate of major hemorrhage in the extended-treatment group, versus a rate of 2.3% in the limited-treatment group.

To examine directly the question of the optimal duration of treatment in the absence of clinical risk factors, a recently published study by Kearon and associates[5] prospectively compared 3 months of oral anticoagulation therapy versus extended anticoagulation therapy in patients with a first episode of idiopathic deep vein thrombosis. The study was terminated early (after an average follow-up of 10.5 months) because of a very significant difference in rates of recurrent thromboembolism in the 2 treatment arms. The rate of recurrent thromboembolism in this prospectively selected and stringently defined set of patients with idiopathic thrombosis was 27.4% per patient-year after 3 months of treatment, versus 1.3% per patient-year in those receiving extended treatment. As in the research by Schulman and colleagues, there were excess episodes of major bleeding in the prolonged-treatment group. Major bleeding occurred at a rate of 3.8% per patient-year in this group, whereas there were no major bleeds in the 3-month group. These results suggest that oral anticoagulation therapy should be extended beyond 3 months in patients after a first episode of idiopathic deep vein thrombosis. Although the authors do not advocate an indefinite duration of anticoagulation therapy, it has been shown that thrombotic events can recur many years after an initial episode;[2] this suggests a potential long-term benefit for continued oral anticoagulation therapy.

The impact of biochemical risk factors is yet to be clearly elucidated with respect to the duration of anticoagulation therapy after venous thromboembolism. It is becoming apparent that clinical risk factors are an important modulator of the risk of recurrent thrombosis, even when certain biochemical anomalies are present.[1,5,6] The exception is the lupus anticoagulant: its presence, or that of an anticardiolipin antibody, appears to be associated with a significant risk of recurrent thrombosis,[5,7] and long-term anticoagulant therapy after an initial thrombotic episode should be maintained in affected patients. Other patients at high risk include those who are homozygous for factor V Leiden or doubly heterozygous for heritable risk factors.[8] No prospective studies to date have assessed the optimal length of anticoagulation therapy in patients heterozygous for factor V Leiden, or for protein C, protein S or an-

tithrombin deficiency. Although recurrent thromboembolism may be more likely in these patients,[9] most centres do not advocate lifelong anticoagulation after a first thrombotic episode unless the initial event was life threatening or, in some cases, where there is antithrombin deficiency.[8] These recommendations may be modified in light of Kearon and associates' findings,[5] which showed that patients with a first idiopathic thrombosis benefited from extended anticoagulation therapy whether they had any underlying biochemical risk factor or not. The factor V Leiden mutation has not been found to be associated with an increased risk of venous thrombosis after hip- or knee-replacement surgery;[6] again, this suggests the importance of clinical circumstances.

Extended anticoagulation therapy, although clearly beneficial in some patients, requires continual monitoring and is not without the risk of minor or major hemorrhage.[1–5] Studies now in progress are evaluating the role of lower intensity long-term oral anticoagulation therapy,[10] which is hoped to provide ongoing protection against recurrent thrombosis, but at a lower cost of hemorrhagic complications.

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Radiofrequency radiation exposure and other environmental concerns

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Environmental and occupational health risks are increasingly a focus of public concern, and busy physicians are now commonly faced with requests for information about the consequences of exposure to chemicals as diverse as dioxin, lead, mercury and pesticides, or to physical agents such as radiation, noise and vibration. Indeed, the results of a recent survey indicated that Canadians rate the medical community as their most trusted source of environmental health information.[1] Family physicians surveyed in Ontario[2] reported that they had fielded questions in the last year related to exposure to specific types of radiation; of those who responded, 88% had been asked about exposure to sunlight, 67% about radiation (presumably ionizing), 40% about electromagnetic fields and 6% about radon.[2] However, these physicians gave low ratings to their own knowledge of most environmental health issues. Clearly, physicians need to be better prepared to respond to the environmental health concerns of their patients and communities.

The research letter by Dr. Artnarong Thansandote and colleagues (page 1311)[3] is helpful in this regard. It presents a clear, succinct summary of an investigation undertaken to address a community's concern about exposure to radiofrequency (RF) radiation. The increased use of cellular telephones has resulted in the installation of numerous radio transmitters to relay calls, thus giving rise to concerns about the emission of RF radiation. Thansandote and colleagues made over 160 measurements of RF power-density levels in areas accessible to teachers and students in 5 Vancouver schools: 3 with a cellular base-station antenna on or near the