Artificial Neural Networks for Anticoagulant Management – Think Again!

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Key words: neural network, warfarin, oral anticoagulants

IMAJ 2004;6:770–771

The number of patients treated chronically with oral anticoagulant drugs has risen dramatically over the past few years. This increase is accounted for both by the increasing number of patients with deep vein thrombosis and pulmonary embolism with underlying thrombophilic states receiving long-term anticoagulation, and an appreciation of the importance of chronic anticoagulation in patients with atrial fibrillation [1]. Over 1 million Europeans take oral anticoagulants daily, and this number may be expected to rise in the future. Although the number of individuals treated chronically with anticoagulants in Israel is unknown, based on data available in the Clalit Health Services database an estimation is possible. In the Sharon area, 2,981 Clalit Health Services patients took oral anticoagulants for at least 6 months in 2003 (Ellis, Hekselman et al., unpublished data). By extrapolation, approximately 36,000 Israelis were treated with oral anticoagulants during that 6 month period.

Oral anticoagulants in clinical use today, the prototype of which is warfarin, work by inhibiting the dynamic interconversion of vitamin K and vitamin K epoxide. This results in the inhibition of carboxylation of the terminal residues of coagulation factors VII, IX, X and prothrombin. Consequently, the concentration of these factors in plasma diminishes and clot (fibrin) formation is impaired. Oral anticoagulants are highly effective in the prevention of thrombotic events: they reduce recurrences of deep vein thrombosis by 85% when used continuously; they result in a 66% relative risk reduction in stroke in patients with non-valvular atrial fibrillation and have recently been shown to be a useful adjunct to aspirin in patients with unstable angina [2]. However, they have unfavorable pharmacodynamics that make their use labor-intensive and troublesome for patients and physicians alike. At the core of the problem lies the great number of variables that affect the bioavailability of the oral anticoagulants. Factors such as diet, medications, intercurrent illnesses – all unavoidably unpredictable in the daily lives of our patients – and genetically determined activity of hepatic cytochromes responsible for warfarin metabolism conspire to make the dosing of the oral anticoagulants subject to frequent change in order to maintain appropriate levels of anticoagulation as determined by international normalized ratio testing. As a result, frequent INR measurements are needed in a large number of patients, while only some maintain a predictable INR with a constant dose of warfarin.

Recently, much attention has been directed at means to improve oral anticoagulant administration with regard to attaining constant therapeutic INR levels. Four treatment frameworks have been studied: *usual care*, which is the office-based management of oral anticoagulant treatment by a primary care physician; *oral anticoagulant clinic* management, which is delivered by specialized practitioners in a clinical environment dedicated to oral anticoagulant therapy and patient-directed care whereby the patient checks his/her INR using a home-based finger-prick test. Thereafter, the patient both reports the result to a physician and receives instructions regarding the appropriate warfarin dose to be taken (termed *patient self-testing*), or makes the decision regarding warfarin dosing alone based on prior experience (termed *patient self-management*). Comparative studies have found both forms of patient-directed care to be the most efficient means of managing oral anticoagulant treatment, followed by oral anticoagulant clinic care, with usual care performing worst of all [3]. This is disconcerting for Israeli practitioners, since the most common means of oral anticoagulant management in this country is "usual care." Only small numbers of patients are self-managed, and oral anticoagulant clinics, while growing in number, are not prevalent.

Enter ... Artificial Neural Networks. The paper in this issue of *IMAJ* by Solomon et al. [4] proposes the use of ANNs as a means of improving the care of patients using long-term warfarin. A word of explanation regarding this futuristic humanoid-sounding technique is in order. An artificial neural network is a computer-based information-processing paradigm that is inspired by the way biological nervous systems process information. The key element of this paradigm is the novel structure of the information processing system. It is composed of a large number of highly interconnected processing elements (neurons) working in unison to solve specific problems. ANNs, like people, learn by example. An

INR = international normalized ratio
ANN = artificial neural network

ANN is configured for a specific application, such as pattern recognition or data classification, through a learning process. Learning in biological systems involves adjustments to the synaptic connections that exist between the neurons. This is true of ANNs as well, where the learning process is termed "training."

ANNs have been used successfully in a number of spheres: in investment analysis to predict the movement of stocks and currencies from previous data, in signature analysis in banking as a mechanism for comparing current signatures with those stored, and as an early detection system to assess the state of aircraft engines by monitoring vibration levels and sound waves. Not surprisingly, ANNs are currently an area of active research in biomedical systems, mainly in the spheres of modeling human body parts and disease recognition based on input in the form of symptoms, physical signs, laboratory and radiologic data. After training, the ANN can be presented with input consisting of a set of symptoms; it will then find the full stored pattern that represents the "best" diagnosis and treatment.

In their study, Solomon and colleagues [4] provided their ANN computer program with a number of key elements needed to predict a maintenance dose of warfarin in 148 patients treated for at least 1 month. The variables chosen were age, gender, height, weight, treatment indication, smoking and drinking habits, concomitant medications, loading warfarin dose, target INR, and maintenance warfarin dose. Of these, age, loading dose of warfarin and the use of amiodarone were found to correlate best with the maintenance dose of warfarin needed to maintain a therapeutic INR. Using these three variables an ANN was constructed to predict the maintenance dose of warfarin and was compared with the predicted dose using a linear regression model. The authors show that both models performed equally well and correlated well with the actual dose of warfarin administered to the patients during the study. By the authors' own admission some important caveats of the study must be acknowledged. First, the number of patients (148) studied is too small to be able to safely conclude that the ANN is a robust tool able to perform accurately in thousands of patients. Furthermore, the most vexing problems of warfarin treatment were not addressed in this study – namely, dietary changes, intercurrent illnesses, and changes in medication use; these are notorious for their disruptive effect on the INR and their unpredictability make them incongruous with predictive models. So it appears at this time that there is no substitution for periodic INR measurements and meticulous dose adjustments in warfarin-treated patients, despite their tediousness.

However, oral anticoagulant management may not always be this way. Recently a plethora of new anticoagulants has entered clinical trials, both for treatment of active thrombosis such as deep vein thrombosis and pulmonary embolism, and for prevention of perioperative thromboembolism and in atrial fibrillation. An important direction in current anticoagulant drug development is the manufacture of orally administered agents with favorable pharmacokinetic and pharmacodynamic profiles that will ultimately compete with and possibly replace the currently used vitamin K antagonist oral anticoagulants. Realization of this goal would simplify long-term anticoagulation immensely. One such drug is ximelagatran, a direct inhibitor of thrombin. Large phase III studies have demonstrated its efficacy in both perioperative venous thromboembolism prophylaxis and in long-term use in deep vein thrombosis and non-valvular atrial fibrillation [5–7]. The drug is licensed for these indications in five European countries, but recently was denied FDA approval in the United States because of a 6% incidence of liver function abnormalities, the long-term significance of which is uncertain [8]. Hot on the heels of ximelagatran are a number of other orally active direct thrombin inhibitors as well as a modified heparin molecule (SNAC-heparin) that is bioavailable orally.

Thus, we may be witnessing an interesting competition between those working to improve current oral anticoagulant drug management, such as Solomon and her colleagues, and those attempting to bring to market alternative oral anticoagulants, designed to avoid the necessity for laborious monitoring processes. This is one race in which no matter who achieves their goal first, we'll all be winners!

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I didn't like the play. But I saw it under unfavorable circumstances – the curtains were up

Groucho Marx (1895-1977), one of the three Marx brothers of vaudeville fame