HEART OF THE MATTER

A Sea Change in Anticoagulation Therapy

For more than half a century, physicians have been struggling with the seemingly impossible task of dosing vitamin K–dependent anticoagulants ever since they were demonstrated to be beneficial in the treatment of acute myocardial infarction.

At that time, the major risk for acute MI was the development of a pulmonary embolism occurring in the setting of weeks of prescribed absolute bed rest. Physicians, patients, and nurses have dealt with the logistical difficulties in managing the narrow dose range required to achieve maximum benefit while minimizing risk. Dose titration walks a fine line between recurrent embolic stroke and major bleed.

BY SIDNEY GOLDSTEIN, M.D.

The slow onset of vitamin K antagonists such as warfarin associated with the variability of dose response driven by genetic polymorphism, food ingestion, and interaction with other drugs has made dosing a therapeutic nightmare. In spite of the problems, vitamin K anticoagulant therapy has remained the standard method for preventing thromboembolism in atrial fibrillation and after valve surgery. The process of dose adjustment for warfarin, the most commonly used drug of this class, requires a huge manpower effort.

Over time, attempts to find an alternative therapy have been unsuccessful. Trials comparing the combination of aspirin and clopidogrel with aspirin alone found the combination more effective than aspirin alone, but not as effective as warfarin.

The comparison of subcutaneously administered factor Xa inhibitors fondaparinux and idraparinux with warfarin resulted in fewer emboli but more bleeding. The long-term subcutaneous administration required with low-molecular-weight heparin also was unacceptable. More recently, the direct thrombin inhibitor ximelagatran was found to have a benefit similar to that of warfarin but with an unacceptable incidence of hepatotoxicity.

For the first time, an effective and safe replacement of warfarin has been developed. The direct thrombin inhibitor dabigatran, a cousin of ximelagatran, was shown to be at least as effective as warfarin and associated with fewer bleeding episodes, depending on the dosage, in the 18,000-patient RE-LY study presented in August at the European Society of Cardiology meeting (CARDIOLOGY NEWS September 2009, p. 1). If further clinical observations support the efficacy and safety of this drug, it will represent a sea change in our management of atrial fibrillation. It will also affect the management of other clinical entities that are prone to develop thromboembolism, such as mechanical nonbiologic valve implantation.

Dabigatran, approved in Canada and Europe, is the first of this class of drugs being developed to provide an opportunity to evaluate other direct thrombin inhibitor molecules. In addition to direct thrombin inhibitors, oral factor Xa inhibitors are under intense clinic evaluation. One of these, rivaroxaban, also approved in Canada and Europe, demonstrated efficacy in prevention of venous thromboembolism following major orthopedic surgery (N. Engl. J. Med 2008;358:2776-86). Like dabigatran, it has a rapid onset of action and can be given orally in a fixed dose, comparable to warfarin with less bleeding. Both direct thrombin and factor Xa inhibitors have been tested in orthopedic patients in whom venous thrombosis can be easily identified with venography. They are yet to be tested more widely in other cardiovascular settings. A number of studies with factor Xa inhibitors are underway to evaluate their benefit in acute coronary syndromes in association with antiplatelet therapy. The clinical comparison of these two new classes of anticoagulants will require further definition.

It is clear that these drugs will change the shape of anticoagulant therapy for a variety of cardiovascular conditions. Many patients undergoing atrial fibrillation ablation may find a safe, easily taken oral medication a better alternative to electrophysiologic intervention. The safety and benefit of these new classes of anticoagulants will make it possible for more patients and physicians to adhere to published guidelines once their efficacy is proved. For now, dabigatran represents a major advance in the prevention of thromboembolism in these patients. ■

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