

FOREWORD

Anticoagulants are the mainstay for prevention and treatment of venous thromboembolism. Heparin and low-molecular-weight heparin (LMWH) are widely used for thromboprophylaxis in general medical and surgical patients. Recent studies indicate that fondaparinux, a synthetic analogue of the pentasaccharide sequence that mediates the interaction of heparin and LMWH with antithrombin, also is effective in these settings. In Europe, LMWH and fondaparinux are the agents most often used for thromboprophylaxis in patients undergoing major orthopaedic surgery. In contrast, in North America, warfarin is used in place of parenteral anticoagulants in at least 50% of these patients. This difference in practice reflects the shorter hospital admissions and the recognition that orthopaedic patients, particularly those undergoing hip arthroplasty or surgery for hip fracture, remain at risk for venous thromboembolism for several weeks after their operation. Although warfarin is easier to administer than LMWH or fondaparinux, which must be given by subcutaneous injection, warfarin requires routine coagulation monitoring, which is inconvenient for patients and physicians. Consequently, there is a need for new oral anticoagulants that produce a predictable anticoagulant response and have a wide therapeutic index so that coagulation monitoring is unnecessary. New oral anticoagulants with these features plus a rapid onset of action also have the potential to streamline treatment of venous thromboembolism. Such agents would obviate the need for subcutaneous injection of LMWH or fondaparinux as initial treatment and would circumvent the routine coagulation monitoring and dose adjustments that are a hallmark of extended therapy with warfarin.

Are we close to having new oral anticoagulants with these characteristics? That is the topic of this supplement. Ximelagatran, the first oral direct thrombin inhibitor, is a promising new agent. A prodrug of melagatran, ximelagatran is easy to use because, when given in fixed doses, it produces an anticoagulant effect within 2h, reflecting the bioconversion of absorbed ximelagatran into melagatran. Melagatran has a half-life of 4-5h, so ximelagatran is given twice daily. No significant food interactions have been detected and ximelagatran has a low potential for drug interactions. Consequently, ximelagatran can be given without coagulation monitoring.

How does ximelagatran address unmet medical needs in the prevention and treatment of venous thromboembolism? Professors Ansell and Bergqvist outline the limitations of current thromboprophylactic regimens, whereas Professor Haas highlights the suitability of thrombin as a target for new anticoagulants, such as ximelagatran. Focusing on orthopaedic surgery, Professor Dahl describes why patients undergoing these procedures require intensive thromboprophylaxis and Dr. B. Eriksson reviews the data with ximelagatran in this setting. Finally, Dr. H. Eriksson summarizes the studies evaluating ximelagatran for the treatment of venous thromboembolism. Building on this database, Dr. Agnelli provides clinical perspective on the future potential of ximelagatran for the prevention and treatment of venous thromboembolism. Thus there is something here for everyone. Whether you are

a surgeon or an internist, ximelagatran will be of interest to you. As the first new anticoagulant to be introduced since the vitamin K antagonists were discovered in the 1940s, ximelagatran holds considerable promise for the future.

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