VENOUS THROMBOSIS TRIALS AT THE METHODIST HOSPITAL IN HOUSTON

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INTRODUCTION

Venous thromboembolism continues to be a significant problem in hospitalized patients.1 According to Geerts et al., "The rationale for thromboprophylaxis is based on the high prevalence of venous thromboembolism among hospitalized patients, the clinically silent nature of the disease in the majority of patients, and the morbidity, costs and potential mortality associated with unprevented thrombi."2,3 Approximately two million Americans suffer from deep vein thrombosis (DVT) each year,4 but because most of these clots are silent, the true incidence is actually unknown. In addition to the acute thrombotic event with its inherent morbidity and time missed from work, the late sequelae from even properly treated thrombi can present as venous stasis and leg ulcers.

Thromboembolic disease is responsible for approximately 200,000 deaths annually in the United States alone.5 The elderly are at highest risk, with a one-year mortality approaching 21%.6 Although excellent drugs are currently available to prevent and treat DVT, an investigation into new drugs with new targets and designer end points of anticoagulation seemed clinically relevant and timely.

The following paper will discuss the different antithrombotic/anticoagulant agents that have been used in clinical trials at The Methodist Hospital in Houston, Texas. Several of the trials have been successfully completed and featured in medical publications such as the *New England Journal of Medicine* and *The Lancet.*

NEW ANTITHROMBOTIC STRATEGIES

According to a review by Hirsh and Weitz, "anticoagulant strategies to block rhrombogenesis have focused on inhibiting thrombin, preventing chrombin generation, or blocking che initiation of coagulation" (Figure 1).[7] The drugs scudied at The Methodist Hospital will be discussed in chronological order, wich che first new class of anticoagulant drugs being one of the Factor Xa inhibitors, pemasaccharide.

FONDAPARINUX

Fondaparinux is the first of a new class of antithrombotics: the synthetic inhibitors of Factor Xa (SIXa). Originally termed ORG31540/SR90107A, fondaparinux is a unique and novel pencasaccharide produced by total chemical synthesis and designed specifically to bind its target, the protein antithrombin, with very high affinity. Fondaparinux (trade name Arixrra) is obtained exclusively by chemical synthesis from basic building blocks synthesized from glucose, glucosamine and cellobiose. Ir has guaranteed barch-ro-batch consistency that eliminates the risk of contamination by pathogenic agems.[8]

Methodist physicians participated in the drug's Phase II and Phase III trials, with ours being the largest enrolling site worldwide in the Phase II Pentathlon trial. Phase 116 studies, which included more than 900 patients undergoing total hip replacement surgery and 400 undergoing knee replacement surgery, demonstrated statistically significant dose-dependent reductions in the risk of D V T with this agent.9

We also participated in a multi-center, double-blinded, dose-ranging Phase II study to determine optimal dosing in 933 patients undergoing primary total hip replacement surgery.10 Figures 2 and 3 outline the efficacy and safety results from this trial.11 Following this were four Phase III trials-randomizing more than 7,000 patients on five continents-which demonstrated that once-daily fondaparinux in a 2.5 mg subcutaneous dose reduced the risk of overall D V T by 50% compared with the established standard of care (enoxaparin) in patients undergoing major orthopedic surgery.[12] These trials provided significant support of fondaparinux and were the basis of eventual F D A approval of the drug in orthopedic populations.

XIMELAGATRAN

A prodrug of the active site-directed thrombin inhibitor melagatran, ximelagatran is absorbed from the small intestine and was the next drug to be studied in orthopedic populations at The Methodist Hospital.13 Ximelagatran has a plasma half-life of three to four hours and was administered in a twice-daily dose. This drug was considered a savior in the anticoagulation world as ir has no food or drug interactions and, due to its very predictable response, did not appear co require any anticoagulant monitoring.

To evaluate the utility of this drug in North American orthopedic populations, we participated in the Platinum hip and knee trials. The Platinum Hip Trial randomized 1,557 patients with adequate venography undergoing total hip replacement to receive oral

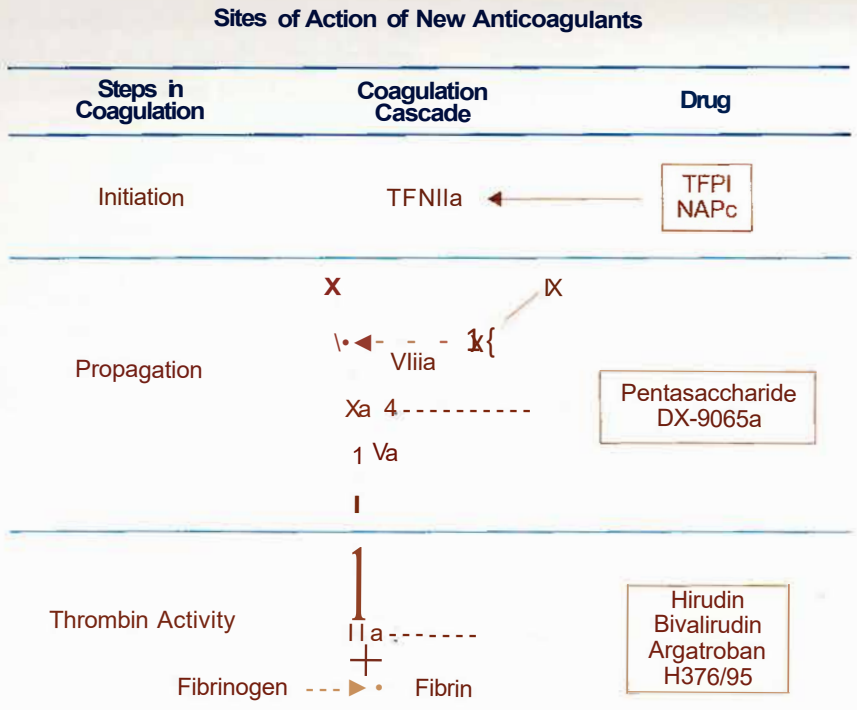

Figure 1. Steps in blood coagulation. Initiation of coagulation is triggered by the factor Vlia/tissue factor complex (VIIafTF), which activates factor IX (IX) and factor X (X). Activated factor IX (IXa) propagates coagulation by activating factor X in a reaction that utilizes activated factor VIII (Vliia) as a cofactor. Activated factor X (Xa), with activated factor V (Va) as a cofactor, converts prothrombin (II) to thrombin (IIa). Thrombin then converts fibrinogen to fibrin. Tissue factor pathway inhibitor (TFPI) and nematode anticoagulant peptide (NAPc2) target VIIafTF, whereas synthetic pentasaccharide and DX-9O65a inactivate Xa. Hirudin, bivalirudin, argatroban, and H376/95 inactivate IIa.

ximelagacran (24 mg cwice daily) or enoxaparin (30 mg SQ cwice daily) for seven to 12 days.14 The results of the trial showed thac enoxaparin was superior to ximelagatran when started postoperatively in the 24-mg, twice-daily dosage. Further trials altered rhe dosages of ximelagatran to 36 mg cwice a day with an additional subcutaneous dose given on rhe day of surgery, which chen demonstrated superiority over rhe enoxaparin regimen.15 However, release of the drug in the U.S. market has been delayed due to FDA safety concerns regarding liver enzyme elevations that occurred in longer-term aerial fibrillation trials.

IDRAPARINUX

A more highly sulfated derivative of fondaparinux, idraparinux is an 'mves-cigarional drug with a half-life of 150 hours. This promising and sophisticated new anticoagulant, to be studied in acute DVT and pulmonary embolism patients, was presenred to us in the Van Gogh crials by Sanofi Aventis. In a Phase II trial performed elsewhere, idraparinux therapy was compared with warfarin therapy in 659 patiencs with acute proximal DVT.[16] After five to seven days of initial treatment with enoxaparin, patiencs were randomized to receive once-weekly subcutaneous doses of idraparinux (2.5, 5.0, 7.5 or 10 mg.) or warfarin for 12 weeks. The primary end point, changes in compression ultrasound or new findings on perfusion lung scans, was similar in all of the idraparinux groups and no different in the warfarin group.[17]

Based on the above results and the face chat there was less bleeding in the lowest-dosage idraparinux group than in the warfarin group, the 2.5 mg, once-weekly dose of idraparinux was chosen for the Phase III trials. The Van Gogh DVT and pulmonary embolism trials are now completed, with the data to be reviewed and published.

SOLUBLE THROMBOMODULIN

The Methodist Hospital was next recruited by the Hamilton, Ontario group to participate in the soluble thrombomodulin trial. Figure 1 reveals where thrombomodulin affects propagation of thrombin. The initiation of coagulation is rriggered by che tissue factor/factor VIia complex char activates factor IX and factor X. Accivated factor IX propagates coagulation by activating factor X in a reaction utilizing factor VIII as a cofactor. Activated procein C chen blocks the propagation of coagulation by inactivating factors Va and VIIIa at the thrombin/chrombomodulin site. Protein C and thrombomodulin also target chis seep: According to Weitz er al., "soluble rhrombomodulin binds thrombin and induces a conformational change in the active site of che enzyme char converts ir inco a potent activator of protein C."[17]

In an open-label, dose-escalating scudy, soluble thrombomodulin positively affected coagulation abnormalities in patients with disseminated imravascular coagulation.18 After these results were demonstrated, the Canadian group organized a Phase II dose-ranging study in patiencs undergoing elective total hip replacement surgery.19 Patients were given chrombomodulin subcutaneously (0.3 or 0.45 mg/kg) cwo to four hours after surgery, and patients receiving the lower rhrombomodulin dosage received anocher dose five days later. The primary end poinc, a composite of venographically detected and symptomatic venous chromboembolism, occurred in only 4.3% of chose patients receiving the lower dose and in none of the 99 patients in che higher-dose

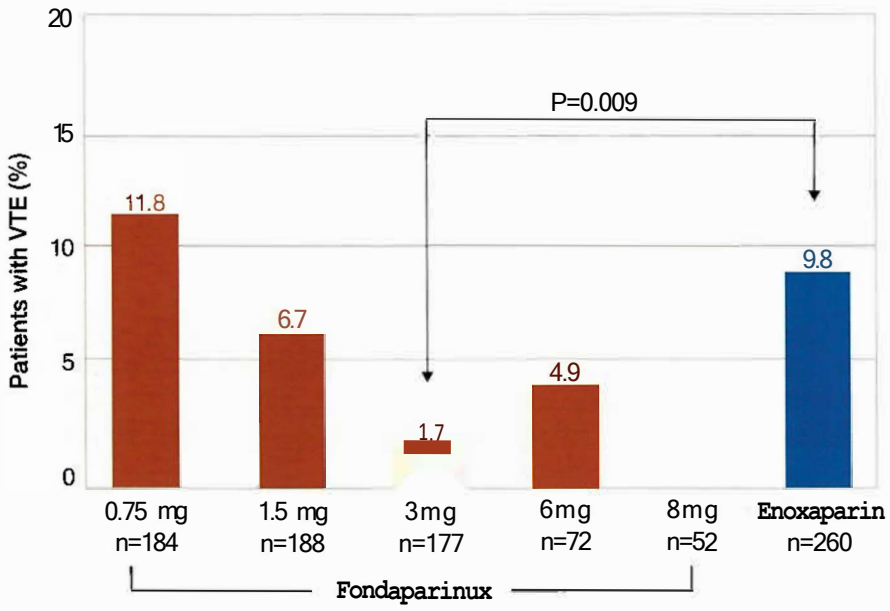

Figure 2. Efficacy results from fondaparinux Phase I dose-finding study in patients with total hip replacement. Data are expressed as percent of treated patients with venous thromboembolism. Enrollment in the 6 mg and 8 mg groups was discontinued early after an increase in bleeding incidence was noted.

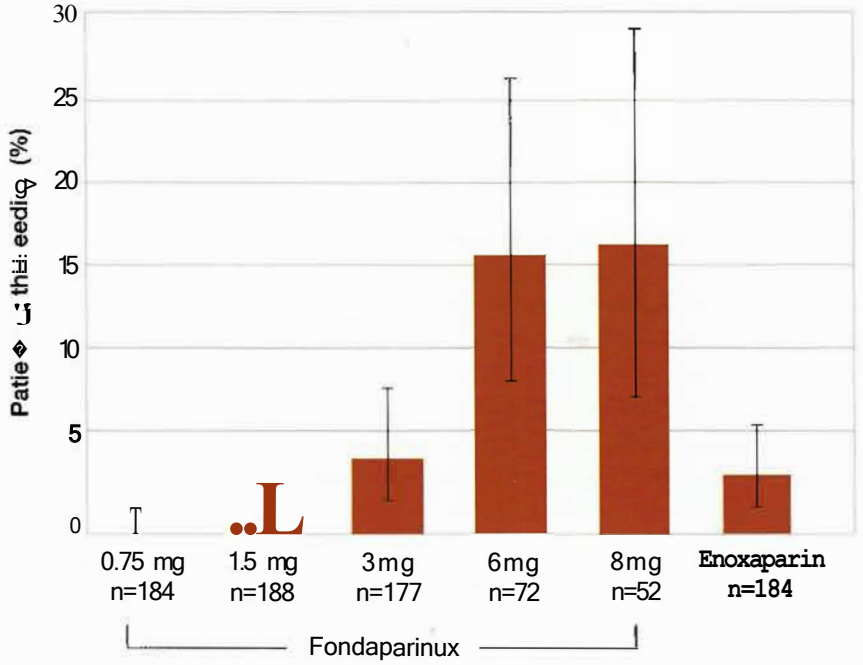

Figure 3. Safety results from fondaparinux Phase I dose-finding study in patients with total hip replacement. Data are expressed as percent of treated patients with major bleeding. Enrollment in the 6 and 8 mg groups was discontinued early because of this complication.

group.[17] Phase III trials will next be required to compare ART-123 (soluble thrombomodulin) to either enoxaparin or fondaparinux.

CONCLUSION

Recently developed, highly selective, novel therapeutic agents such as those explored in our trials can optimize antithrombotic efficacy and improve the prevention of hemorrhagic complications. It is hoped that The Methodist Hospital's participation in several landmark trials - with particular attention to patient care and safety - will lead to the development of new and possibly better ancicoagulancs that ultimately have a positive benefit for the future of medicine.

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