



the
changing face
of anticoagulant therapy

Improving the Management of Patients at
Risk for Venous Thromboembolism

ASHP *Advantage* E-Newsletter

Spring 2010

Tips for Managing Anticoagulation in Health Systems and Update on Emerging Anticoagulants

Questions about the use of established and emerging anticoagulants to prevent venous thromboembolism (VTE) and Joint Commission requirements for anticoagulant therapy were discussed in a live webinar conducted on January 21, 2010, to follow up a Midday Symposium on the topic held at the 44th ASHP Midyear Clinical Meeting and Exhibition in Las Vegas, Nevada, on December 8, 2009. A web-based activity based on the symposium is available at www.ashpadvantage.com/vte. The faculty shared practice “pearls” based on their extensive experience with participants in the live webinar, and many of these practice pearls were described in a previously released newsletter available at <http://www.ashpadvantage.com/vte/vte-winter-newsletter.pdf>. Additional tips for the managing anticoagulation in health systems and an update on emerging anticoagulants are provided in this newsletter.

Dabigatran and desirudin are emerging direct thrombin (factor IIa) inhibitors, and rivaroxaban is an emerging oral direct factor Xa inhibitor. Although desirudin was approved by FDA in 2003, it only recently became available on the U.S. market in March 2010.

Question: Why isn't warfarin used more often for VTE prophylaxis after elective total knee or hip replacement surgery?

Evidence-based guidelines of the American College of Chest Physicians (ACCP) recommend warfarin as a possible option for VTE prophylaxis in this patient population.¹ According to ACCP, the target range for the international normalized ratio (INR) for VTE prophylaxis is 2.0 to 3.0, which is the same as the target range used for VTE treatment.^{1,2} Lower target INR ranges (e.g., 1.5-3.0) that are not well documented in the literature have been used successfully during warfarin therapy for VTE prophylaxis and a variety of other indications.³⁻⁵ The target range of 1.5 to 2.0 has not been studied in comparative trials. Uncertainty about the appropriate target INR range to use may contribute to decisions to avoid using warfarin for VTE prophylaxis. However, the logistical difficulty of monitoring INR values on a long-term outpatient basis may be a larger factor. Dr. Dager noted that in his experience, the primary reason that warfarin is not used more often for VTE prophylaxis after major orthopedic surgery is the need for cumbersome laboratory monitoring.

Faculty

Stuart T. Haines, Pharm.D., BCPS, FCCP, FASHP, FAPhA, Activity Chair
Professor and Pharmacotherapy Specialist
University of Maryland School of Pharmacy
Baltimore, Maryland
Clinical Specialist
West Palm Beach VA Medical Center
West Palm Beach, Florida

William E. Dager, Pharm.D., BCPS, FCSHP, FCCP, FCCM
Pharmacist Specialist
UC Davis Medical Center
Clinical Professor of Pharmacy
University of California, San Francisco, and Touro School of Pharmacy
Clinical Professor of Medicine
University of California, Davis
Sacramento, California

Toby C. Trujillo, Pharm.D., BCPS
Associate Professor
University of Colorado Denver School of Pharmacy
Clinical Specialist – Cardiology/
Anticoagulation
Director of Inpatient Anticoagulation –
Thrombosis Management Service
University of Colorado Hospital
Aurora, Colorado

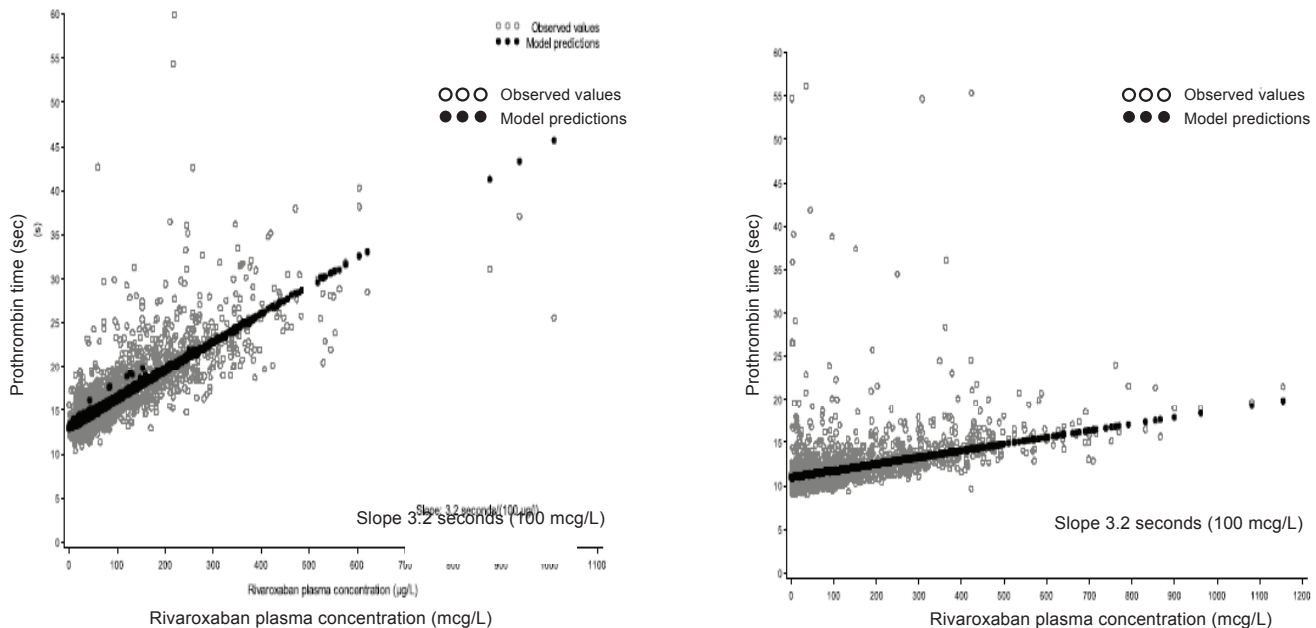
Question: The lack of laboratory monitoring during use of emerging anticoagulants is a purported advantage over warfarin, but some clinicians have suggested monitoring the prothrombin time (PT) or other clotting assays in patients with renal dysfunction who are receiving these drugs. Is this practice recommended?

While the use of common laboratory coagulation assays to monitor for abnormal or unexpected responses to emerging anticoagulants appears logical, much more research is needed before this practice can be recommended. In the case of dabigatran, approximately 80% of an oral dose is eliminated renally.⁶ The commonly available clotting assays (e.g., PT, activated partial thromboplastin time [aPTT]) are not particularly useful for monitoring dabigatran therapy in patients with renal impairment because the assays are not sensitive (to PT) or do not correlate in a linear fashion with changes in plasma drug concentration (aPTT).⁷ Dabigatran plasma concentrations do correlate well with the thrombin time and the ecarin clotting time; however, these assays are not readily available for use in the clinical practice setting.

Rivaroxaban also relies on the kidneys for elimination, although to a lesser extent than dabigatran.⁶ The PT correlates with rivaroxaban concentration in a linear fashion, but large changes in plasma drug concentration are associated with small changes in PT (i.e., the PT lacks sensitivity).⁸ Moreover, there is considerable variability in the relationship between PT and plasma drug concentration depending on the reagent used (Figure 1). An assay and reagent with greater sensitivity (i.e., one for which small changes reflect small changes in drug concentration) is needed for monitoring purposes. Therefore, PT monitoring at this time is not useful during rivaroxaban therapy in patients with renal dysfunction because it may not accurately reflect drug exposure.

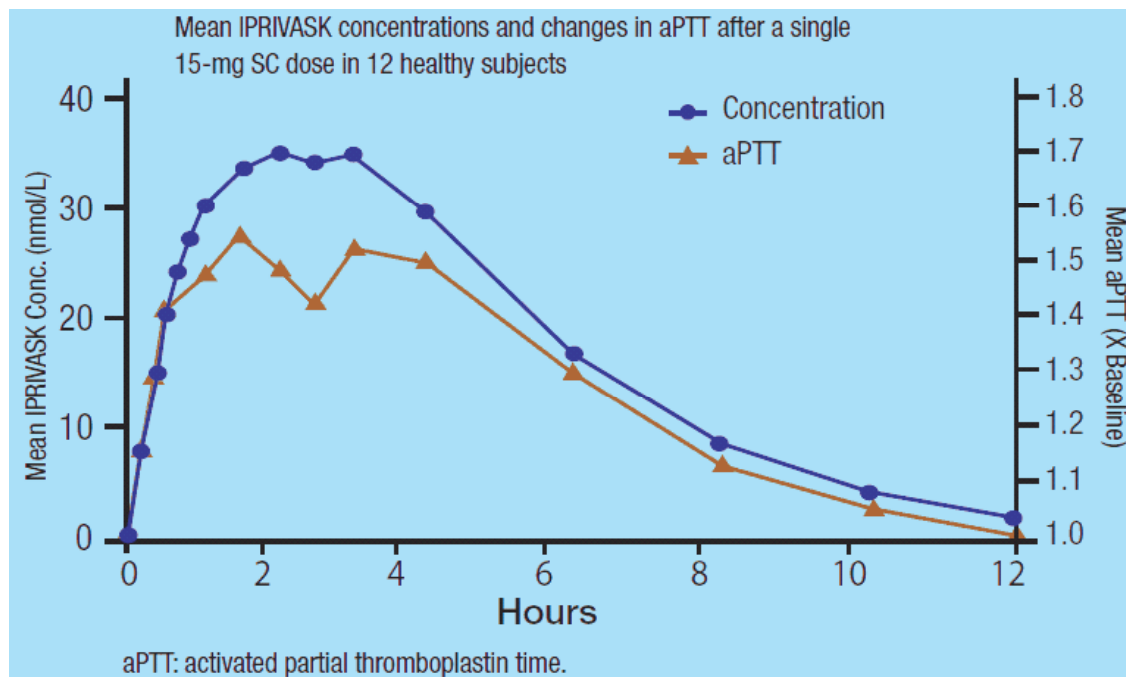
Figure 1. Rivaroxaban Effect on Clotting Assays: Two Different Reagents

Adapted from reference 8.



The direct thrombin inhibitor desirudin is markedly affected by renal impairment.⁹ The aPTT appears to be the clotting assay that correlates most closely with desirudin plasma concentrations. Changes in the aPTT observed after a single 15-mg subcutaneous dose of desirudin correlated closely with changes in plasma drug concentrations in healthy volunteers (Figure 2), suggesting a role for aPTT monitoring during desirudin therapy in patients with renal impairment.¹⁰ Current labeling recommends that the aPTT should not be prolonged greater than 2 times the baseline when desirudin is used for prophylaxis of VTE.

Figure 2. Desirudin Effect on Clotting Assays



Question: The Joint Commission's National Patient Safety Goal (NPSG) 03.05.01 (formerly known as 3e) requires medical center-approved protocols for the management of anticoagulation. Does The Joint Commission require physicians to document reasons for deviation from the medical center-approved protocols?

Element of performance 2 for the Joint Commission's NPSG 03.05.01—reduce the likelihood of patient harm associated with the use of anticoagulant therapy—requires the use of approved protocols for the initiation and maintenance of anti-coagulant therapy.¹¹ Separate protocols must address each condition for which the drug is used (e.g., VTE, atrial fibrillation).¹² This requirement applies primarily to the use of anticoagulants for the treatment of VTE. It does not apply to situations in which short-term anticoagulation is used for VTE prevention, and the clinical expectation is that the patient's laboratory values for coagulation will remain within, or close to, normal values.

In evaluating compliance with element of performance 2 for NPSG 03.05.01, Joint Commission surveyors require a measure of success (MOS), which is a quantifiable measure that demonstrates whether an action was effective and sustained. The MOS goal is the quantifiable level of compliance (expressed as a percentage) that the organization strives to achieve. The method of evaluation, source(s) of data to be used, and frequency of evaluation must be documented. Because NPSG 03.05.01 has a direct impact (i.e., is likely to create immediate risks to patient safety, and the risks stem from a lack of processes), noncompliance with this element will place the institution at moderate risk of losing accreditation.

A well written protocol based on the best available evidence can be applied in the great majority of cases – but not all. Occasional deviations should be anticipated but the frequency of these deviations should be lower than the MOS goal. While not required, it is in the best interests of the institution to document the reason for deviating from an approved protocol for anticoagulant therapy in each case. The institution should be prepared to reprimand or discipline prescribers who routinely deviate from approved protocols. On the other hand, if many or most practitioners are routinely deviating from these protocols, there may be legitimate reasons and the institution should revise their protocols with practitioner input.

“ Protocols should provide procedures to follow for the safe and effective delivery anticoagulant therapy; protocols are not intended to provide a cookbook approach to patient care. ”

—Stuart T. Haines, Pharm.D., BCPS, FCCP, FASHP, FAPhA

Question: What approach should be used to provide VTE prophylaxis in patients with heparin-induced thrombocytopenia (HIT)?

Heparin-induced thrombocytopenia (HIT) is a rare immune-mediated adverse effect associated with unfractionated heparin (UFH) and low molecular weight heparin (LMWH) therapy that increases the risk for thrombosis.¹³ This condition is of concern when providing VTE prophylaxis in a variety of patient scenarios that were described by Dr. Dager. Patients may present with acute (i.e., new onset) HIT in an initial phase with a low platelet count or in a recovery period after discontinuation of heparin during which the platelet count is increasing toward normal. The risk for thrombosis is particularly high in the initial phase and less so in the recovery phase.

A patient may experience isolated HIT (i.e., HIT without thrombosis) or heparin-induced thrombosis-thrombocytopenia syndrome (commonly referred to as HITTS) characterized by HIT-related thrombosis. Isolated HIT may require anticoagulation for 1 month while HIT with thrombosis, including HITTS, may require 3 or more months of anticoagulation. Patients with a history of HIT of more than 3 months without thrombocytopenia when they present with a need for VTE prophylaxis (e.g., after major orthopedic surgery) may not be at additional risk compared with heparin naïve patients, although alternative options can be considered.

The timing of HIT development with respect to heparin exposure is classified as rapid if it is nearly immediate (i.e., within hours) with recent heparin exposure, although it typically is 5-10 days.¹³ Delayed HIT can develop within 40 days after stopping heparin.

According to Dr. Dager, decisions about VTE prophylaxis in one of these clinical scenarios involving HIT depend on the platelet count (and trends in its recovery after discontinuing heparin), how long risk factors for

thrombosis have been or will be present, the presence of risk factors for bleeding, and the costs of treatment and laboratory monitoring. Anticoagulant options for thromboprophylaxis in patients with HIT include direct thrombin inhibitors, warfarin, and fondaparinux. LMWH cannot be used in a patient with HIT after receiving UFH because of cross reactivity of HIT antibodies formed during UFH exposure with LMWH.¹³ Direct thrombin inhibitors usually are used initially for thromboprophylaxis in patients with HIT. The direct thrombin inhibitor lepirudin may be given by subcutaneous (s.c.) injection every 12 hours.¹⁴ Desirudin, another direct thrombin inhibitor given by s.c. injection, has been used in patients with HIT.¹⁵ The high cost of injectable direct thrombin inhibitors may be a consideration in their use.

“ The approach to VTE prophylaxis in a patient with heparin-induced thrombocytopenia requires an individualized approach, taking into consideration the platelet count, risk for thrombosis and bleeding, and costs of treatment and laboratory monitoring. ”

—William E. Dager, Pharm.D., BCPS, FCSHP, FCCP, FCCM

Warfarin may be used after recovery of the platelet count. Bridge therapy with a direct thrombin inhibitor often is used because of the lag time after warfarin initiation before therapeutic effects are evident.

Fondaparinux is an alternative for patients with HIT who require prophylaxis for VTE, although it has rarely been linked to HIT-type reactions and thrombosis.¹⁶ If fondaparinux is chosen, the VTE prophylaxis (not treatment) dosage (2.5 mg/day) is given.

Question: Aside from bleeding, what other toxicities have been reported with the emerging direct thrombin inhibitors and direct factor Xa inhibitors?

Hepatotoxicity is a potential concern with emerging anticoagulants because of problems with ximelagatran, an oral direct thrombin inhibitor that the Food and Drug Administration (FDA) considered approving in 2004. The drug showed promise for the prevention and treatment of VTE and the prevention of stroke in patients with atrial fibrillation in clinical trials, and short-term data showed that the drug was well tolerated.¹⁷⁻¹⁹ However, long-term data revealed an increased risk for liver injury that could lead to serious liver disease.²⁰ The drug was never approved in the United States because an FDA advisory panel concluded that the benefits did not outweigh the risks. Ximelagatran was withdrawn from the worldwide market in 2006 because of toxicity.

The incidence of liver enzyme elevations was lower with dabigatran than enoxaparin in clinical trials comparing the two drugs for VTE prevention.²¹ Dabigatran was no more likely than warfarin to be associated with liver enzyme elevations in a clinical study comparing the two drugs for stroke prevention in patients with atrial fibrillation.²² In four VTE prevention studies of more than 10,000 patients, the most commonly reported adverse effects from dabigatran were related to bleeding and occurred in 14% of patients.²¹ The incidence of bleeding was similar to that in the control group receiving enoxaparin (13%). In the study of patients with atrial fibrillation, dyspepsia was more common in dabigatran-treated patients (12%) than in warfarin-treated patients (6%).²²

In three VTE prevention studies of 4571 patients receiving rivaroxaban for up to 39 days after hip or knee replacement, bleeding occurred in approximately 3.3% of patients, a rate that was similar to that in enoxaparin-

treated patients.²³⁻²⁶ Other common adverse effects from rivaroxaban were nausea, increased gamma-glutamyl transpeptidase, (a biliary excretory enzyme), and increased transaminases. The incidence of liver enzyme elevations was no higher with rivaroxaban than enoxaparin in clinical trials comparing the two drugs for VTE prevention in patients undergoing major orthopedic surgery.²⁷

Fewer safety data are available for desirudin than for rivaroxaban and dabigatran. It is unclear whether desirudin has any effect on liver function according to the current labeling. The most commonly reported non-hemorrhagic adverse effects with desirudin include nausea, anemia, deep thrombophlebitis, wound secretion, and injection site mass. None of these adverse effects appear to be appreciably different compared with unfractionated heparin or enoxaparin. Allergic reactions were reported in 2% of patients who received the drug in clinical trials.

In summary, the incidence of commonly reported adverse effects is similar with these emerging anticoagulants and established anticoagulants. Neither rivaroxaban nor dabigatran appears to be associated with hepatotoxicity.

“ The emerging direct thrombin inhibitor dabigatran and direct factor Xa inhibitor rivaroxaban do not appear to be associated with hepatotoxicity. ”

—Toby C. Trujillo, Pharm.D., BCPS

New Educational Opportunity

An *AJHP* supplement entitled “Improving anticoagulant use for prevention of venous thromboembolism” will be published with the May 15, 2010 issue and mailed to ASHP members. The supplement, which provides 2.5 hours (0.25 CEU) of continuing pharmacy education credit, will also be available on the activity portal at www.ashpadvantage.com/vte.

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