

2006 marked the 40th year of publication for *The Annals*. Throughout its history, *The Annals* has provided important contributions to the development of clinical pharmacy. In 2007, we are continuing to publish articles reflecting on the history of clinical pharmacy through the eyes of practitioners, including those pioneering clinical pharmacy, as well as those who have more recently entered the profession and a well-established specialty. In addition, we are presenting articles and editorials from the early history of *The Annals* that have given direction and shape to the practice of clinical pharmacy (see page 496).

Advances in Anticoagulation Management: The Role of Pharmacy

Maureen A Smythe

Over the past 40 years, major changes have occurred in the area of anticoagulation management. New strategies have been developed for older anticoagulants, older beliefs have been challenged, new anticoagulants have been introduced, and new indications have been identified for existing anticoagulants. The role of the pharmacist in managing anticoagulant therapy has been established, and clinicians have learned more about the critical importance of medication safety. Advances have spanned from the outpatient setting to the critical care setting.

Until the mid-1980s, the primary anticoagulants in use were unfractionated heparin and the coumarins or vitamin K antagonists. Heparin was first discovered to have antithrombotic properties in 1916. In the late 1960s, it was discovered that heparin acted by enhancing the activity of antithrombin. Despite decades of experience with heparin, controversies surrounding its use remain. Limitations in the use of the activated partial thromboplastin time (aPTT) test for heparin monitoring have been well recognized for a number of years.¹ Currently, there is wide variation among hospitals in their approach to heparin monitoring.^{2,3} Some investigators/clinicians have advocated moving from use of the aPTT for heparin monitoring to use of a heparin anti-Xa level.⁴ Outcomes data to support such a move are lacking. In addition to uncertainty about the best approach to monitor heparin, the data to support a well-established therapeutic range for heparin (something we learned in pharmacy school) have also been scrutinized.⁵ Although a recent trial found that un-

monitored administration of subcutaneous heparin plus warfarin was equivalent to low-molecular-weight heparin (LMWH) plus warfarin, further studies are needed to establish the safety and efficacy of unmonitored heparin therapy.⁶

The first report of the clinical use of warfarin as an anticoagulant was in 1941. More than 40 years later, we learned the importance of differences in the sensitivity of commercial thromboplastin reagents used in the measurement of the prothrombin time (PT). In the 1980s, most US laboratories used thromboplastin reagents with an international sensitivity index (ISI) of 1.8–2.4, while laboratories in European hospitals used more responsive reagents with an ISI of 1.0–1.4. These differences in reagent sensitivity led to significant differences in dose requirements when warfarin was monitored using the PT ratio. The international normalized ratio (INR) was introduced in the late 1980s as a way to correct for varying thromboplastin reagent sensitivity. The INR is now the standard test for warfarin monitoring. Another advance in oral anticoagulant therapy was the recognition of genetic polymorphisms, including a mutation in the gene coding for CYP2C9. This mutation significantly reduces the metabolism of the more potent *S*-warfarin, which reduces warfarin dose requirements.

An understanding of the specific manner in which heparin binds to antithrombin led to the development of newer classes of antithrombotic agents. Introduced in the 1980s, the LMWHs (which are basically “little” heparins, about 1/3 the molecular weight of heparin) have reduced binding to proteins, resulting in a more predictable pharmacokinetic response. Although one of the original benefits of LMWHs was that monitoring was not required, we are hearing more and more about the need to monitor LMWHs in special patient populations. Fondaparinux, approved in 2001, was the

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first agent in a new class of antithrombotics known as indirect inhibitors of factor Xa.

The direct thrombin inhibitors (DTIs) are another new class of anticoagulants introduced in the 1990s after years of investigation into the anticoagulant properties of the saliva of the *Hirudo medicinalis* leech. The initial use of a medicinal leech for bloodletting dates back to early Egyptian times. In 1833, when leech use was at its peak, the annual use of leeches in France approached 100 million. Although use declined by the end of the 19th century, leeches are again coming into favor in the area of reconstructive microsurgery. Although there are over 700 species of leeches, *H. medicinalis* is preferred due to its ability to bite deeply and cause prolonged bleeding. Hirudin is one of the salivary products secreted by the *H. medicinalis*. Lepirudin (recombinant hirudin) was the first DTI released in the US, followed by argatroban and bivalirudin. As these agents are costly, their use is primarily in the management of heparin-induced thrombocytopenia and as an anticoagulant in patients undergoing percutaneous coronary intervention.

Ximelagatran, the first oral DTI, was rejected by the Food and Drug Administration due to concerns regarding hepatotoxicity; it was subsequently withdrawn from the worldwide market. Dabigatran, another oral DTI, is currently in Phase III trials. If this agent is approved, the number of outpatients taking warfarin could be impacted, as monitoring is not required with dabigatran.

Although newer anticoagulants (LMWHs, fondaparinux, DTIs) offer advantages, their lack of complete reversibility can pose challenges in the face of overanticoagulation. Other anticoagulant agents in development include a once-weekly, indirect-acting pentasaccharide inhibitor (idraparinux), direct-acting pentasaccharide inhibitors (apixaban, rivaroxaban), soluble thrombomodulin, and tissue pathway factor inhibitor.

Over the last 2 decades, the benefit of pharmacist-managed anticoagulant therapy has been well established. In 1985, *Drug Intelligence & Clinical Pharmacy* published an article on cost justification of a pharmacist-managed anticoagulation clinic.⁷ Therapy management by pharmacists resulted in an improvement in the percentage of prothrombin times and INRs in the therapeutic range and a reduction in hospitalizations for thromboembolic or bleeding events. The anticoagulation clinic was found to have a favorable cost:benefit ratio. Numerous publications since that time have also confirmed these benefits.

The pharmacist's role in managing anticoagulation therapy in the inpatient setting has also been established. An evaluation of over 700 000 Medicare patients from almost 1000 hospitals found that those without pharmacy-directed heparin and warfarin management had higher mortality rates, length of stay, Medicare charges, bleeding rates, and transfusion requirements.⁸ Pharmacy-managed anticoagulant therapy improves the quality and safety of such therapy in the inpatient and outpatient setting.

Several other major developments in the area of anticoagulation have occurred. Hypercoagulable states have been identified, along with an understanding of their role in causing thromboembolism. The optimal use of antiplatelet agents (with or without combination anticoagulant therapy) in arterial disease has been further defined. Efforts aimed at public awareness of the signs of stroke have paved the way for the timely use of thrombolytic therapy for acute ischemic stroke. The introduction of newer, longer-acting anticoagulants administered subcutaneously shifted the treatment of venous thromboembolism (VTE) to the outpatient setting. The introduction of warfarin self-monitoring for select patients has allowed for even further empowerment of patients. The introduction of recombinant Factor VIIa for hemophilia patients with inhibitors of Factor VIII or IX was a major breakthrough. Despite the cost and thrombotic risk associated with this agent, its off-label use continues to increase in many clinical settings, including traumatic bleeding and uncontrollable hemorrhage. Understanding the link between activation of inflammation and coagulation led to the development and approval of drotrecogin alfa, activated for acute severe sepsis.

The importance of evaluating hospitalized patients for the risk of VTE has received considerable attention and will continue to be a major area of focus for the healthcare system in the coming decades. VTE is the most common form of preventable hospital death, causing more deaths annually in the US than breast cancer, AIDS, or motor vehicle accidents. The death of NBC news correspondent David Bloom helped increase public awareness of the risks for VTE. The Coalition to Prevent DVT, a group of national medical societies, patient advocacy groups, and public health organizations, was formed to help make deep vein thrombosis a major public health priority.

The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and the National Quality Forum have defined 8 performance measures currently in testing on VTE risk assessment, prevention, and treatment⁹:

RISK ASSESSMENT/PROPHYLAXIS

1. VTE risk assessment/prophylaxis within 24 hours of hospital admission;
2. VTE risk assessment/prophylaxis within 24 hours of transfer to the intensive care unit;

TREATMENT

3. Documentation of inferior vena cava filter indication;
4. VTE patients with overlap therapy;
5. VTE patients receiving unfractionated heparin with platelet count monitoring;
6. VTE patients receiving unfractionated heparin management by nomogram/protocol;
7. VTE discharge instructions;

OUTCOME

8. Incidence of potentially preventable hospital-acquired VTE.

These measures will be finalized and released by early 2008. Hospital performance on these quality measures will appear on consumer Web sites. Insurance providers have already begun to require participants to submit quality indicators in the area of VTE as a pay-for-performance measure.

Over the past 2 decades, the importance of medication safety with anticoagulants became a critical issue for health systems. In the 1980s, the increased incidence of spinal hematomas in patients receiving LMWH and neuraxial anesthesia heightened awareness of the potential significant risks with anticoagulant therapy. The move toward computerized physician order entry will help in the continuing reduction of drug errors and interactions with anticoagulants. JCAHO has included anticoagulants in its proposed 2008 National Patient Safety Goals, while the Institute for Healthcare Improvement has called for improvement in the use of anticoagulant drugs in its 5 Million Lives Campaign.

As the role of the pharmacist in anticoagulation management continues to evolve, pharmacists must keep current with therapeutic advances. For pharmacists working primarily in the area of anticoagulation, a national certification examination is available from the National Certification Board for Anticoagulation Providers. Individuals completing this certification are identified by the initials CACP (Certified Anticoagulation Care Provider). Available resources to help pharmacists stay current in the area of anticoagulation include:

1. The American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines. The first conference proceedings were published as a supplement in *Chest* in 1986.¹⁰ The guidelines are updated approximately every 3–4 years.
2. The American Society of Health-System Pharmacists Antithrombotic Pharmacotherapy Traineeship was launched in 1985 and involves an intense self-study, didactic component as well as a 5 day experiential program.
3. The Anticoagulation Forum is a multidisciplinary network of clinicians involved in managing anticoagulant therapy. Founded in 1991, the forum now has more than 3000 members from over 1300 anticoagulation clinics worldwide.
4. ClotCare Online Resource, founded by Henry Bussey PharmD and his daughter, Marie Bussey Walker. The site (www.clotcare.com) provides information for patients and healthcare practitioners about thrombotic disorders and therapeutic issues involving anticoagulant and antiplatelet therapy, among others.

5. American College of Clinical Pharmacy Anticoagulation Training Program, which is offered in conjunction with the University of Texas and the Anticoagulation Clinics of North America. This program involves a minimum of 4 weeks of intensive training.

6. Numerous online anticoagulation courses and certificate programs are available.

The last 2 decades have brought numerous advances in the field of anticoagulation. The future will see an increased focus on patient safety and disease prevention. Quality care as it relates to anticoagulation therapy will be tied to hospital accreditation and reimbursement. New classes of anticoagulants will be introduced, which will heighten the need for reversal agents. Pharmacists will continue to play a critical role in managing and assessing the outcomes of anticoagulant therapy in the future. The eventual impact of oral DTIs on pharmacist-managed anticoagulation clinics remains to be seen.

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