College of American Pathologists Conference XXXI on Laboratory Monitoring of Anticoagulant Therapy

Introduction

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Thromboembolism is a common clinical problem that is associated with serious morbidity and mortality if not appropriately treated. For nearly 50 years, the therapy of venous thromboembolism has centered around the use of heparin and warfarin. Use of these agents has always presented a double-edged sword; too little anticoagulation is associated with a higher risk of recurrent thrombosis, while too much anticoagulation is associated with a higher risk of bleeding. Thus, laboratory tests were introduced at an early point to monitor the therapy of these 2 agents; indeed, laboratory monitoring of anticoagulant therapy is one of the oldest forms of therapeutic drug monitoring.

Heparin and warfarin have traditionally been monitored with global assays of coagulation, such as the prothrombin time, the Lee-White clotting time, and the activated partial thromboplastin time (aPTT). These tests were introduced before the pharmacology of these agents and the nature of the tests were fully understood, in part because it was felt that the degree of prolongation of these global tests reflected the degree of antithrombotic activity of the drugs. Since their introduction into clinical usage, considerable progress has been made in our understanding of the pharmacology of these agents. During this time, new insights into the laboratory tests used to monitor these agents have also been gained.

Comparison of clinical trials of oral anticoagulant therapy conducted in the United States and Europe during the 1970s and early 1980s demonstrated that oral anticoagulant therapy in the United States was associated with a higher rate of bleeding. This was ultimately linked to differences in the average dosage of oral anticoagulants administered, with the dosage being related to the prothrombin time used to monitor these patients.[1] It became apparent that there were significant discrepancies between the prothrombin times obtained using American versus European reagents. A method was devised to calibrate the response of prothrombin time reagents so that a uniform measure of anticoagulation could be reported by all laboratories; thus was born the international normalized ratio (INR).[2] Although first recommended in 1983, the INR was not widely adopted in the United States until the 1990s. As might be expected, adoption of the INR system has not been without its own share of problems.

Development of a uniform method of monitoring oral anticoagulant therapy has permitted a more thorough evaluation of the appropriate target range for therapy. Careful epidemiologic studies have shown that an INR of at least 2.0 is needed for effective antithrombotic therapy for most indications.[3] The risk of bleeding increases with an increasing INR, but appears to increase dramatically above an INR of 4.5 to 5.0.[3] These observations have permitted development of effective recommendations for use of oral anticoagulants in a variety of clinical settings.

Perhaps the most common test used to monitor heparin therapy after its introduction into clinical medicine was the Lee-White blood clotting time. Those of us who are old enough to remember this test understand the source of the enthusiasm for the aPTT after its introduction in the 1970s. Despite more than 20 years of experience with this assay, there are still significant questions regarding its use for monitoring heparin therapy. It has become clear that the response of individual aPTT reagents to heparinization varies significantly, and thus a uniform therapeutic range based on either an aPTT in seconds or a ratio of patient to normal aPTT is not valid for all reagents.[4] Attempts to develop a calibration system analogous to the INR have been unsuccessful to date.[5] These problems have contributed to the confusion regarding the optimal therapeutic range for heparin and the optimal method of monitoring therapy.

The recent addition of low-molecular-weight heparin has added another twist to the heparin story. This new agent appears to be effective in a variety of clinical settings.[6] However, questions remain regarding the role of laboratory monitoring of low-molecular-weight heparin therapy. Additional agents, such as danaparoid, hirudin, and argatroban, have been recently approved or are expected to be approved for clinical use in the near future. It is becoming clear that now, more than ever, the laboratory plays a critical role in the clinical care of patients with thromboembolic disease, but that the laboratory's role is changing rapidly.

The College of American Pathologists Conference XXXI, held in October 1997, was convened to address many of the issues related to the laboratory monitoring of anticoagulant therapy. The objectives of this consensus conference were to review the mechanism of action of various anticoagulants, discuss current issues in the laboratory monitoring of these agents, make recommendations to im-

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prove laboratory monitoring of these agents, and to look down the road to new antithrombotic agents that are being introduced into clinical medicine with an eye on the role of the laboratory in monitoring these agents. Our hope is that the recommendations from this conference will lead to more consistent and improved monitoring of anticoagulant therapy.

Four subcommittees were formed to address specific issues related to anticoagulant therapy. The first group focused on oral anticoagulant therapy and was headed by Robert Fairweather, MD.[7] The second group focused on unfractionated heparin and was headed by John Olson, MD, PhD.[4] The third group focused on low-molecular-weight heparins and recently introduced agents and was headed by Michael Laposata, MD, PhD.[8] The fourth group was charged to look at anticoagulant agents that are in development; this group was headed by Edwin Bovill, MD.[9] Broad representation at the conference was achieved through participation of experts in laboratory medicine, general internal medicine, hematology, cardiology, pharmacy, international standardization, and basic research.

Each group was charged to thoroughly review the literature concerning laboratory issues regarding their anticoagulant agent(s) and to make recommendations regarding the monitoring of therapy based on published reports. Levels of evidence to support the recommendations were defined and were based on the strength of the data in the literature. The working groups each prepared a draft document with its recommendations and circulated this to all participants before the conference. The recommendations were then presented and thoroughly discussed during the conference; a vote was taken following the discussion. The recommendations provided in the following reports all achieved greater than 80% consensus, and most were unanimously accepted.

We believe that the recommendations coming from this consensus conference will have a significant impact on the laboratory monitoring of anticoagulant therapy. We also realize that this conference is not the end of the discussion on this important topic. As is evident from the final section of this conference, there are many new potential agents on the horizon, each directed at a critical step in the hemostatic response to vascular injury. Many of these agents will require some type of monitoring to maximize safety and effectiveness. In this vein, we hope that the accompanying reports stimulate further discussion among all of those interested in this important clinical problem.

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References

1. Poller L, Taberner DA. Dosage and control of oral anticoagulants: an international collaborative survey. *Br J Haematol.* 1982;5:479–485.

2. WHO Expert Committee on Biological Standardization. 33rd Report. *World Health Organ Tech Rep Ser.* 1983;687:81–105.

3. Hirsh J, Dalen JE, Deykin D, Poller L, Bussey H. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest.* 1995;108(suppl): 231S–246S.

4. Olson JD, Arkin CF, Brandt JT, et al. College of American Pathologists Conference XXXI on laboratory monitoring of anticoagulant therapy: laboratory monitoring of unfractionated heparin. *Arch Pathol Lab Med.* 1998;122:782–798.

5. Van der Velde EA, Poller L. The APTT monitoring of heparin—the ISTH/ICSH collaborative study. *Thromb Haemost.* 1995;73:73–81.

6. Weitz JL. Low-molecular-weight heparins. *N Engl J Med.* 1997;337:688–698.

7. Fairweather RB, Ansell J, van den Besselaar AMHP, et al. College of American Pathologists Conference XXXI on laboratory monitoring of anticoagulant therapy: laboratory monitoring of oral anticoagulant therapy. *Arch Pathol Lab Med.* 1998;122:768–781.

8. Laposata M, Green D, Van Cott EM, Barrowcliffe TW, Goodnight SH, Sosolik RC. College of American Pathologists Conference XXXI on laboratory monitoring of anticoagulant therapy: the clinical use and laboratory monitoring of low-molecular-weight heparin, danaparoid, hirudin and related compounds, and argatroban. *Arch Pathol Lab Med.* 1998;122:799–807.

9. Bovill EG, Mann KG, Phillips D, Vlasuk G, Becker RC. College of American Pathologists Conference XXXI on laboratory monitoring of anticoagulant therapy: future directions. *Arch Pathol Lab Med.* 1998;122:808–816.

COLLEGE OF AMERICAN PATHOLOGISTS CONFERENCE XXXI

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