Prevention of Bleeding in Older Patients Taking Warfarin

TO THE EDITOR: The well-designed study by Beyth and colleagues (1) showed that major bleeding events decreased significantly among older patients who received long-term oral anticoagulation through a multicomponent program that included patient self-testing, as compared with patients who received usual medical care prescribed by the treating physician. However, the study prompted the fundamental question of how this intervention would compare with what is rapidly becoming an important practice in many U.S. health care centers: nurse- or pharmacist-managed anticoagulation management services (AMS). The benefits of AMS over usual medical care, in terms of improved clinical outcomes (reduction in major bleeding and recurrent thromboembolic events) and improved efficacy of anticoagulant monitoring (length of time that the international normalized ratio [INR] remains therapeutic), have been well documented in the medical and pharmacy literature (2–5). Indeed, the major bleeding rate of 5.6% at 6 months seen in the intervention group in Beyth and colleagues’ study is still quite high when compared with major bleeding rates of 0% to 2.4% in outcome studies of AMS (2–4). Beyth and colleagues found that the anticoagulant effect was controlled in 56% of the intervention group; this finding is similar to figures approaching 60% with AMS (5).

Studies from our institution’s AMS, a pharmacist-managed anticoagulation clinic in a managed care setting that serves more than 1300 enrolled patients receiving long-term oral anticoagulation, have shown similar results. During a 12-month period in 1999, the major bleeding rate was 2.2% (29 of 1317 patients) among all enrolled patients, and 56% of patients remained within the defined therapeutic INR range (unpublished data).

Although the external validity of their methods and outcome assessments could be argued, Beyth and colleagues’ study does not seem to present compelling reasons why a multicomponent, comprehensive anticoagulant management program should be preferable to an existing or proposed AMS.

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References

TO THE EDITOR: The paper by Beyth and colleagues (1) described a clever innovation that attempts to circumvent the delay that bedevils the process of transmitting the results of prothrombin testing from the laboratory to the provider, who then chooses the appropriate warfarin dose. Indeed, this home monitor is similar to the glucometer used by patients with diabetes.

While applauding this innovation, however, I wish to reiterate my observations (2) favoring extra monitoring for patients taking long-term warfarin therapy and suggesting that the fecal occult blood test and tests for hematocrit are two additional monitoring tools that could improve patient outcomes when used in conjunction with prothrombin activity (INR) measurements. Indeed, these tests are routinely used to screen patients for anticoagulant therapy (3).

The fecal occult blood test yields negative results even in patients receiving warfarin therapy (4). A positive result, therefore, should prompt a search for the cause of bleeding. Beyth and colleagues found that the gastrointestinal tract was the most common site of bleeding, as did other authors studying similar patients (5). This test, therefore, is pertinent. Patients can easily learn how to complete Hemoccult (Beckman Coulter, Fullerton, California) cards every 4 to 6 weeks and take or mail them to the laboratory for analysis.

A decreasing hematocrit level may indicate bleeding or occult hemolysis in patients with prosthetic heart valves (2). Either way, appropriate work-up should be done to discover the explanation. One venipuncture should yield enough blood for both the INR and the hematocrit measurements.

The authors could not have included hematocrit in their protocol because the home portable monitor presumably lacks the capability for this test. However, it is possible that major bleeding...
episodes in both patients and controls would have been reduced if these additional monitoring tools had been used.

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References

IN RESPONSE: We appreciate the comments of Dr. Spyropoulos and agree that there is compelling evidence of the benefits of specialized programs that coordinate management of anticoagulant therapy over “usual care” (1). In addition to the health benefits, the potential economic benefits of an organized process of care for anticoagulant therapy have been noted (2). Since we did not have a nurse- or pharmacist-managed AMS available at our institution, we cannot make any direct comparisons between our intervention and such a management service.

Regarding Dr. Kajubi’s comments, we did not routinely measure hematocrit levels in our study, and the portable monitors we used measured only the INR. As noted in our study and others (3), most anticoagulant-related bleeding is gastrointestinal. Furthermore, occult upper gastrointestinal lesions are often “unmasked” when patients receive anticoagulant therapy (4, 5). In contrast, specific causes of lower gastrointestinal bleeding during anticoagulant therapy are identified less often. Before routinely including fecal occult blood testing in the management of all patients treated with long-term anticoagulant therapy, its potential health and economic benefits should be formally studied.

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References

Inflation of Precision in Medical Reports

TO THE EDITOR: It is somewhat amusing to see reports in which values are presented with nonsensical levels of precision, such as a serum creatinine concentration of 450.8 μmol/L and a bilirubin level of 738.7 μmol/L (1), a glucose level of 15.26 mmol/L (2), 11,823 molecules of CCR5 per cell (3), and medical costs of $37,610 for drug therapy (4). Where did that last 0.8 μmol/L of creatinine, 0.7 μmol/L of bilirubin, 0.06 μmol/L of glucose, 3 molecules of CCR5 per cell, and $10 of cost come from? I suppose that they all were created by a calculator or a spreadsheet. That does not mean that they have any significance when the precision of typical laboratory measurements is a coefficient of variation of 1% to 5% and estimates of costs are rarely precise to within 10%. Loss of perspective about the actual precision of values seems to be common in Annals and other medical journals. To avoid confusing ourselves and readers about the ever-expanding number of digits, authors and editors should return to common sense and elementary-school arithmetic when reporting numbers of significant figures. Perhaps my daughter’s sixth-grade arithmetic class could agree to serve as referees in the appropriate rounding of values.

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References
Severe Liver Injury

TO THE EDITOR: We read with interest the study by Reinus and colleagues on hepatitis after treatment with zafirlukast, a leukotriene receptor antagonist (1). In our practice, we encountered a case of fulminant hepatic failure related to zafirlukast in a patient who eventually required liver transplantation. A 36-year-old firefighter had accidental smoke inhalation in May 1999. She received a diagnosis of "industrial asthma" and was prescribed zafirlukast, 20 mg twice daily, which she took regularly. Her other medications included inhalation aerosols, theophylline, and an over-the-counter weight-loss preparation called Lipokinetics, none of which are hepatotoxic.

In June 2000, she presented with nausea, anorexia, and jaundice. Results of tests for hepatitis A, B, and C markers were negative. All drugs were withdrawn immediately. Within 3 weeks of presentation with an acute hepatitis-like illness, the patient developed fulminant hepatic failure. Total bilirubin level peaked to 478.8 μmol (28 mg/dL) (normal range, 5.1 to 17 μmol [0.3 to 1 mg/dL]), prothrombin time peaked to 33.2 seconds (normal range, 10.5 to 13.0 seconds), aspartate aminotransferase level peaked to 45.99 μkat/L (2759 U/L) (normal range, 0 to 0.58 μkat/L [0 to 35 U/L]), and alanine aminotransferase level peaked to 52.26 μkat/L (3135 U/L) (normal range, 0 to 0.58 μkat/L [0 to 35 U/L]). Peripheral eosinophilia was not observed. The patient underwent orthotopic liver transplantation, and the explanted liver demonstrated submassive necrosis.

Our patient was similar to patient 2 in the report by Reinus and colleagues in that she developed fulminant hepatic failure and had liver transplantation. However, our patient did not have hypersensitivity manifestations. In addition, the long interval between initiation of drug therapy and onset of hepatitis suggests an idiosyncratic intermediate metabolite-mediated hepatic necrosis. The development of severe hepatitis-like illness with dramatic onset of fulminant hepatic failure reinforces the need for monitoring hepatic biochemical tests in patients taking zafirlukast. The Physicians’ Desk Reference recommends that only patients who are symptomatic or have suspected liver dysfunction be evaluated for liver disease (2). This approach may not be adequate because hepatic dysfunction may progress despite withdrawal of the drug.

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References

Correction: Ivermectin Dose in Update in Dermatology

In the Update in Dermatology (1), the ivermectin dose listed for Chouela and colleagues’ study (2) should be 150 to 200 μg/kg of body weight, not 150 to 200 mg/kg.

References

Correction: Sprout-Associated Infections

In a recent article on sprout-associated infections (1), the last two sentences of the second paragraph in the Discussion section should be: “For sprout grower B, we found the outbreak strain of S. Senftenberg in animal feed from Oregon and Washington, supporting our hypothesis that the source of contamination for outbreak 3 was clover seed from Oregon. Finally, for sprout grower C, two outbreak-associated strains of Salmonella (S. Havana and S. Cubana) were found in seed lots used by this sprout grower.”

Reference