

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Recommendations on Bleeding and Nonbleeding Complications of Vitamin K Antagonists

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H&O What is the impetus for issuing guidelines on the pharmacology and management of vitamin K antagonists?

JA Warfarin, the commonly used vitamin K antagonist in North America, requires intensive management to maintain patients in the therapeutic anticoagulant range as measured by the International Normalized Ratio (INR). There are many complexities and controversies about management, and to guide physicians, the American College of Chest Physicians has sponsored a consensus conference to develop guidelines on such therapy. A group of recognized experts has convened approximately every 3–4 years over the last 20 years to update these guidelines. The conference not only establishes guidelines for the vitamin K antagonists, but addresses the entire field of antithrombotic drugs, their indications and proper use. The process involves an extensive and thorough review of the literature and discussion to arrive at a consensus, especially when the scientific literature is incomplete and there is controversy pertaining to a particular agent. What eventually develops are consensus guidelines shaped as much as possible by evidence-based literature. The next guideline update is in process, with plans for publication in the first quarter of 2008. The last group meeting and publication was in 2004.

H&O What are some of the major recommendations that will be published in 2008?

JA With regard to warfarin therapy, the recommendations will focus on how best to administer this drug and manage its complications, as well as its specific indications, including atrial fibrillation, venous thromboembolism, and mechanical heart valves. One chapter is devoted entirely to the pharmacology and the management of warfarin therapy. The chapter discusses the exciting advances made in the field of pharmacogenetics to better guide warfarin therapy. However, because there is not yet strong enough evidence that such information will improve the outcomes of therapy, the experts take a cautious view with regards to pharmacogenetic-based dosing. There is new evidence emerging regarding the use of very small doses of vitamin K on a daily basis to stabilize therapy in those patients who are unstable, and recommendations are made regarding such therapy. The consensus group also makes recommendations about the importance of a systematic and organized approach to managing therapy such as what occurs in an anticoagulation clinic and discusses the strong evidence in favor of patient self-monitoring of therapy with point-of-care INR hand-held monitors. In the upcoming guidelines, there is a new chapter focused entirely on the management of the interruption of warfarin therapy when a patient needs to undergo an invasive procedure, so-called “bridging” therapy. This chapter also includes recommendations for the management of antiplatelet therapy in patients who need to interrupt therapy for a procedure.

H&O What are the specific recommendations regarding bleeding complications of therapy with vitamin K antagonists?

JA The incidence of major bleeding in patients treated with warfarin is strongly dependent on the quality of dose management and the time that patients stay within the therapeutic INR range. With optimal care, the frequency is approximately 1–2% per year in a cross section of patients on warfarin. In some studies, major bleeding rates as high as 8% per year have been noted, especially with suboptimal dose management. Bleeding is also noted to be more frequent in the first few months following the initiation of treatment, in patients with multiple comorbidities, and in older patients. When major bleeding occurs, treatment is focused on immediate reversal of the

warfarin effect (ie, returning the INR to normal) and support of the patient with whatever blood products may be needed. Warfarin's effect can be reversed by administering fresh frozen plasma at a dose of 15–30 mL/kg, which will replace the vitamin K–dependent coagulation factors. One also administers intravenous vitamin K to hasten the synthesis of new vitamin K–dependent factors, as the transfused factors will dissipate according to their metabolic half-life. Sufficient production of new factors takes a minimum of 12–24 hours if there is no liver impairment. For life-threatening bleeding, one is advised to administer prothrombin complex concentrates (containing the vitamin K–dependent coagulation factors) as a high concentration of factors can be given in a small volume compared to the volume required to deliver the same concentration of factors in fresh frozen plasma. Recombinant factor VIIa has also been shown to rapidly reverse the anticoagulant effect of warfarin, but the half-life of the infused factor VIIa is quite short and dosing may need to be repeated. Vitamin K should also be given as noted above.

H&O Do the guidelines discuss nonbleeding complications of therapy with vitamin K antagonists?

JA Because the nonbleeding complications of therapy are uncommon, there is little discussion of these problems. Warfarin-induced skin necrosis is one such complication, but it is quite rare. When it occurs, it is usually during the initiation phase of therapy (first few days) and is caused by small vessel thrombosis, usually confined to the subcutaneous tissue in fatty areas of the body (eg, buttocks, breasts, abdomen, thighs). In many cases, it is attributed to a transient hypercoagulable state early in therapy due to a reduction of protein C or protein S, two vitamin K–dependent, naturally occurring anticoagulants also reduced by warfarin therapy. Another rare problem that has been attributed to warfarin is hair loss or alopecia. If one examines the literature closely, however, it has never been definitively proven that warfarin therapy causes hair loss. Still, many practitioners believe there could be a causal association. One of the problems with alopecia is that many patients who begin warfarin therapy do so after a major illness, and the trauma or shock to the body of the illness may affect the cycle of hair growth such that hair loss occurs 2–3 months later. When hair loss does occur, it is usually mild and does cease, even with continued warfarin therapy.

Another presumed side effect of warfarin is the rare occurrence of a skin rash. In some cases this has been attributed to the dye contained in different tablet strengths and it is often worth a trial of one of the tablet strengths that does not contain a dye (ie, white tablet).

In some instances, alternative coumarin products may be recommended.

An unusual and uncommon syndrome called the “purple toe” syndrome has been attributed to warfarin therapy. This is a spasmodic and/or embolic phenomenon, sometimes attributed to cholesterol crystals that embolize to the digits, usually the toes.

Finally, patients will present with other vague complaints that they relate to warfarin therapy such as fatigue or headaches. It is always difficult to pinpoint the cause of these nonspecific symptoms, but most practitioners do not believe that they are related to warfarin therapy.

H&O How are the recommendations stratified?

JA Recommendations are based on the strength of the evidence, and they are graded as A, B, or C and also given a qualifying number, either 1 or 2. The strength of the recommendation is designated by the number, and it is derived from the consensus of the panelists involved. If the panelists are certain that the benefits do, or do not, outweigh the risks and burdens of a particular treatment, then they will make a strong recommendation (Grade 1) in favor or against, depending on the benefit or lack thereof. If the benefits and risks or burdens are finely balanced or there is an appreciable uncertainty about the magnitude of the benefits and risk, then the recommendation would be weak (Grade 2). The letters designate the methodologic quality of the supporting evidence. For instance, a Grade A recommendation indicates that there are randomized, controlled trials that demonstrate the outcomes, and that these trials are without important limitations in terms of design. In some cases, a Grade A recommendation can result from overwhelming evidence from large observational studies, rather than randomized, controlled trials. Grade B recommendations result from randomized trials with certain important limitations, meaning that some of the trials addressing a particular issue have inconsistent results or that important methodologic flaws exist in the trials. Grade B recommendations can also result from strong, but not overwhelming, evidence from observational trials. A Grade C recommendation is generally one derived from observational studies or case series. In each of these grades, the strength is qualified with either a 1 or 2 rating.

H&O Could you discuss the future of the management of therapy with vitamin K antagonists?

JA Although the vitamin K antagonists have been around since the 1940s, and there are no other oral anticoagulants,
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new aspects of these drugs are being identified regularly. One of the important topics being assessed now is the value of pharmacogenetics in the dosing of warfarin. Genetic polymorphisms (or mutations) in the genes coding for the enzymes that metabolize warfarin or the protein that is the target of warfarin's action may significantly affect one's response to the drug. There is active research to determine if dosing, and thus therapeutic effectiveness, and outcome can be improved by knowledge of these polymorphisms. Another area of active interest is patient self-monitoring and dose management, much as a patient with diabetes would do with insulin management. Clinical trials indicate that this type of management will improve outcomes, but such therapy in the United States is slow to catch on, and lack of third-party reimbursement is a major barrier to more widespread use.

Beyond the vitamin K antagonists, there are a number of new oral anticoagulants in Phase II and III clinical trials for most of the thromboembolic indications, especially venous thromboembolism and atrial fibrillation. These new drugs are selectively targeted to inhibit a specific coagulation factor, mostly activated factor X or II. Because they have predictable pharmacokinetics, monitoring is not required. If these drugs prove to be safe and effective, as early studies suggest that they are, they will have a significant effect on use of the vitamin K antagonists. Because of ease of use and lack of monitoring

or dose management, these agents have great potential to improve the treatment of thromboembolic disorders and the quality of life of patients.

Suggested Readings

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