All About Warfarin: The Basics

By James R. Roberts, MD

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Learning Objectives: After reading this article, the physician should be able to:
1. Discuss the basic indications of warfarin therapy in the emergency department.
2. Describe the nuances of administering warfarin therapy to emergency patients.
3. Summarize the complications of warfarin therapy in the emergency department.

Release Date: January 2007

It would be an unusual shift when an emergency physician did not encounter a patient taking warfarin. The drug is omnipresent, and it is both a life-saver and a killer. The clinical indications are many, but the complications are gargantuan. Most emergency physicians have a limited knowledge of the nuances of warfarin therapy, and primarily just understand bleeding complications. The literature on warfarin drug-drug interactions, initiation and reversal of coagulopathy, and a plethora of related issues is so vast that no emergency physician can possibly read or totally remember it all.

This month’s column begins a discussion on the clinical issues involving warfarin therapy and its complications as they relate to the emergency physician. Although we rarely start the drug, we frequently must deal with its therapeutic use and untoward sequelae. In a recent column I discussed head trauma in patients anticoagulated with warfarin, and concluded that banging your head and taking warfarin is a bad combination. Seemingly minor head trauma, especially in the elderly anticoagulated patient, is a minefield in which one must tread quite carefully. Although we may not prescribe the drug in the ED, we do prescribe many drugs and offer advice on medical issues that may interfere with the proper use of this anticoagulant.

This month’s column is a basic discussion on the drug itself, highlighting how it is generally used in the population that might frequent your ED. Because warfarin is a drug associated with rather high outpatient morbidity (bleeding complications are reported in up to 10 percent of users), the prescient clinician should be well versed in its use and misuse of this drug.

Medication Guide: Coumadin Tablets
Bristol-Myers Squibb
Pharma Co.
April 2006
www.fda.gov/cder/Office/ODS/MG/warfarin-MG.pdf

These clinical guidelines for using Coumadin (warfarin sodium tablets) on the Food and Drug Administration web site are provided by Bristol-Myers Squibb, and are essentially the same as a package insert. The company produces warfarin as tablets and for injections. (I never knew that IV Coumadin existed.) The guidelines are primarily for physicians, but also are educational fodder for the general public. If you’re prescribing warfarin or dealing with patients who take this drug, you must be aware that patients and their families have access via the Internet to sophisticated medical information. If a layperson suspects Lyme disease as the cause of his headache, a Google search often precedes a physician visit. Armed with knowledge previously only privy to physicians, the public expects doctors to be up on the latest tests, diagnoses, and treatments. Sometimes they know more about a drug than we do, particularly when they are dealing with a loved one’s untoward event or an unpleasant interaction with their own doctor.

This particular publication begins with a bold black box warning about bleeding risks, the first thing an inquisitive patient sees. I have included the actual warning in a table for those who do not think that their patients are not informed consumers.

Coumadin is the brand name for crystals of warfarin sodium. It is an anticoagulant that acts by inhibiting the vitamin K-dependent coagulation factors.

Warfarin stops clotting in the body by inhibiting the normal protective coagulation system that keeps patients from spontaneous bleeding or bleeding more seriously when a blood vessel is injured. This drug is supplied in 1, 2, 2.5, 3, 4, 5, 6, 7.5, and 10 mg tablets.

Warfarin inhibits the synthesis of factors II, VII, IX, and X and also the production of other vitamin K-dependent anticoagulants, such as proteins C and S. (Proteins C and S keep you anticoagulated, and a deficiency of this protein predisposes to thrombosis.) The drug’s biochemical effect is gradual, orderly, and predictable. Warfarin sequentially depresses coagulation factors, starting with factor VII followed by protein C, and ending with factor II activity. The degree of depression on production of these factors is dependent on the dose of warfarin administered. It takes approximately 24 hours after drug administration for an anticoagulation effect to occur. In some instances, the peak anticoagulation effect may be delayed for 72 to 96 hours. The duration of action of a single dose of warfarin is two to five days. The effects of warfarin can become more pronounced as the effects of daily maintenance doses overlap.

Importantly, warfarin has no effect on an established thrombus. It cannot reverse ischemic tissue damage. The goal of anticoagulant therapy is to prevent further extension of a thrombus or to prevent its initial occurrence. Warfarin will prevent further extension of a formed clot (but only after at least 24 hours), and may prevent secondary thromboembolic complications.

Warfarin is totally absorbed within four hours of oral administration. Importantly, warfarin crosses the placenta and concentrations of warfarin in the fetal blood system approach maternal values. Warfarin is not excreted in human milk, so it is not a problem during lactation. Warfarin is inactivated by metabolism in the liver by the cytochrome P-450 system, so changes in liver function and enzyme induction will affect warfarin activity. Inactive metabolites are excreted in the urine.

Patients over 60 often exhibit greater than expected anticoagulation responses to a dose of warfarin, the cause being unknown. Curiously, Asian patients may require lower initiation and maintenance doses of warfarin and appear to have increased sensitivity to the drug. Because warfarin is metabolized in the liver to inactive substances, no dosage adjustment is necessary for patients with renal failure. Hepatic dysfunction (congestive heart failure, hepaticitis, liver toxins) can potentiate the response to warfarin because these conditions exaggerate the already impaired synthesis of clotting factors. With liver dysfunction, there is decreased metabolism of warfarin.

Warfarin has many therapeutic advantages and is indicated for a variety of diseases. Any beneficial effect is weighed against the risk of bleeding. Warfarin can save your life, or take it, and one must pay clinical homage to the

Continued on next page
**Guidelines for Warfarin Anticoagulation**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Duration of Therapy</th>
<th>Suggested INR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DVT/PE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reversible risk</td>
<td>3 months</td>
<td>2.5 (2.0-3.0)</td>
</tr>
<tr>
<td>Idiopathic cause</td>
<td>6-12 months</td>
<td>Same</td>
</tr>
<tr>
<td>Two or more episodes</td>
<td>Indefinite</td>
<td>Same</td>
</tr>
<tr>
<td>Presence of antiphospholipid antibodies</td>
<td>12 months to indefinite</td>
<td>Same</td>
</tr>
<tr>
<td>Deficiency in protein C or S, Factor V, Leiden mutation, homocysteinemia</td>
<td>6-12 months to indefinite</td>
<td>Same</td>
</tr>
<tr>
<td><strong>Atrial Fibrillation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonvalvular or mitral stenosis (Lower levels may be efficacious if bleeding occurs.)</td>
<td>Indefinitely</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation (if high risk with prior TIA/ischemic CVA, system embolism, over 75 years old, severe impaired LV function/CHF)</td>
<td>Indefinitely</td>
<td>2.0-3.0</td>
</tr>
</tbody>
</table>

**Mechanical and Bioprosthetic Heart Valves (varies with valve type)**

<table>
<thead>
<tr>
<th>Valve Type</th>
<th>Duration of Therapy</th>
<th>Suggested INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. Jude Medical bi-leaflet aortic valve</td>
<td>Indefinitely</td>
<td>2.5 (2.0-3.0)</td>
</tr>
<tr>
<td>Bioprosthetic mitral and aortic valves, for three months post-op</td>
<td>Indefinitely</td>
<td>3.0 (2.5-3.5)</td>
</tr>
<tr>
<td>Various mechanical mitral valves</td>
<td>Indefinitely</td>
<td>3.0 (2.5-3.5)</td>
</tr>
<tr>
<td>Caged ball/caged disc valves in combination with aspirin</td>
<td>Indefinitely</td>
<td>3.0 (2.5-3.5)</td>
</tr>
</tbody>
</table>

**Mechanical and Bioprosthetic Heart Valves**

- A reduction in the risk of death, recurrent MI, and stroke after myocardial infarction.
- A significant reduction in stroke, but most studies deal with patients with atrial fibrillation with valvular heart disease.
- Major bleeding episodes can occur with relatively low INR as low 2.0 may be effective.
- There is a significant reduction in bleeding complications with a lower INR. It is assumed that warfarin will provide a similar benefit in patients with atrial fibrillation with valvular heart disease, but most studies deal with patients with nonvalvular AF.
- Myocardial Infarction: Warfarin has been studied as a post-MI intervention for its effect on total mortality and recurrent infarction. In addition, a reduction of cerebral vascular accidents following MI has been noted. Not all post-MI patients are prescribed warfarin, and daily small doses of aspirin often suffice.

**Atrial Fibrillation**: Warfarin reduces the risks of systemic thromboembolism, including stroke, in patients with atrial fibrillation. The total risk reduction is significant, ranging from 60 percent to 85 percent. In AF trials, major bleeding occurred in up to three percent of patients. The reduction in thromboembolic events can occur with relatively minimal inhibition of the clotting system, and an INR as low 2.0 may be effective.

**Indications and Usage**

There are three major indications for warfarin use:

- **Prophylaxis and treatment of venous thrombosis and pulmonary embolism.**
- **Prophylaxis or treatment of complications associated with atrial fibrillation and cardiac valve replacement.**
- **A reduction in the risk of death, recurrent MI, and stroke after myocardial infarction.**

One relative contraindication to warfarin is any condition or risk of hemorrhage greater than the potential benefit of anticoagulation. Importantly, warfarin is contraindicated in pregnant women because the drug crosses the placental barrier, and can cause fatal hemorrhage to the fetus in utero. There are birth malformations in children born to mothers who are treated with warfarin during pregnancy, including central nervous system, the placental and variety of organ abnormalities. Still birth and spontaneous abortion occur more frequently in patients treated with warfarin.

Obviously patients who recently had surgery, are about to have surgery of the central nervous system or eye, or will have other major surgery will have hemorrhagic tendencies, often severe, if they are treated with warfarin. Patients with pericarditis, gastrointestinal bleeding, however, aortic dissection, ruptured aneurysms, and bacterial endocarditis all fare more poorly if they are anticoagulated with warfarin. Other contraindications include threatened abortion, inability to perform INR testing, or unsupervised patients who are elderly, psychotic, alcoholic, or have other conditions where they won’t cooperate with testing and follow-up. Patients who are taking warfarin should not have a spinal puncture or other invasive therapeutic procedures where there is potential for uncontrolled bleeding.

There is an unusual and rare complication of warfarin that results in necrosis or gangrene of the skin or other soft tissue. This is not a hypersensitivity or allergic reaction but an actual local thrombosis and tissue necrosis. It usually occurs within the first few days of anticoagulation therapy when protein C levels are depressed, producing a hypercoagulable state. There is no good treatment for this condition.

One of the biggest problems with warfarin therapy is the drug's narrow therapeutic index, and the drug's activity is affected by a variety of factors, including other drugs and dietary vitamin K sources. The dosage must be controlled and altered by continual determination of the INR or PT test.

A relatively obscure problem with warfarin anticoagulation is the drug's ability to release afterthromatic plaque emboli, resulting in systemic cholesterol microembolism, known as the purple toe syndrome. The purple toe syndrome, a condition I have never seen or heard about, is characterized by dark purplish mottled toes, occurring within three to four weeks after warfarin initiation. Occasionally gangrene may occur.

A number of factors, alone or in combination, are responsible for an increased INR response following warfarin therapy. The main problem with drug interactions is an increase in the anticoagulation effect. The number of drugs causing this are too numerous to mention. Other mechanisms include enzyme induction, enzyme inhibition, and alterations in protein binding, parameters that can either increase or decrease the intended activity of warfarin. A combination of factors and unpredictable drug interactions mandate frequent INR monitoring in patients who will be on long-term medication. A future column will be devoted to interactions with warfarin activity.

A few other risks that should be well known to physicians are the increased potential for bleeding in elderly or debilitated patients, platelet dysfunction, intravenous injections, and increased bleeding tendencies in patients who are treated with NSAIDs and aspirin. Dietary sources of vitamin K will interfere with activity of warfarin; large amounts of green leafy vegetables particularly will provide enough dietary vitamin K to ameliorate anticoagulation. My patients love kale and collard greens, rich sources of vitamin K, but I never see a warning sign in the cafeteria.

**Dosage/Administration**

Warfarin use varies according to the pathologic condition being treated. The accompanying table outlines the indications and the target INR, which for DVT/PE, AF, and post-MI is 2.5, with the acceptable range being 2.0 to 3.0. The target INR for patients with heart valves is slightly different, and varies with the specific valve type. Importantly, an INR greater than 4.0 provides no additional therapeutic benefit in the vast majority of patients, and is clearly associated with a higher risk of bleeding.

When initiating therapy, a large loading-dose can increase the risk of hemorrhage, and does not offer any more rapid protection against thrombosis. Although previously recommended, large loading doses of warfarin are no longer standard. In general, the initial therapy should be 2 mg to 5 mg per day with dosing adjustments based on INR. The maintenance dose for most patients is between 2 mg and 10 mg daily. Some tablets may be cut in half, but many strengths are available. Indications of therapeutic response is dependent on the underlying condition.

If a dose is missed, that dose should be taken as soon as possible on the same day, but patients should not double the daily dose to make up for missed doses. The depression of vitamin K-dependent factors is reflected in an increase in prothrombin time (PT). A system to
standardize the PT for warfarin therapy was introduced by the World Health Organization in 1982, and is based on determination of an international normalized ratio, otherwise known as the INR. The INR provides a common basis for communication of PT results and interpretation of therapeutic ranges. INR has replaced the PT, and there is no reason to order both tests. The INR is generally ordered daily after the initial dose to establish a therapeutic range, and this range has been reached. Subsequent INR determinations are based on a number of factors. It is usually acceptable to check the INR within a range of one to four weeks once a stable dose has been determined. Patients taking warfarin will be subjected to laboratory evaluation for the length of therapy.

Surgical Interventions

Patients undergoing surgery or dental procedures may suffer excessive bleeding if their INRs are elevated. If the procedures are minimally invasive and the patient is under prolonged anticoagulation, preoperatively adjusting the dose to the low end of the therapeutic range, rather than discontinuing the drug may safely allow for continued anticoagulation. Under ideal conditions, surgery can be performed without undue risk of hemorrhage even though the patient is maintained with some degree of anticoagulation.

The major anticoagulant effect of warfarin is delayed up to 24 to 36 hours, and heparin is the preferred intervention when rapid anticoagulation is required. The complete conversion to warfarin can be done quite rapidly, although commonly delayed for three to six days. These guidelines advise continued full heparin therapy (overlapping warfarin therapy with the heparin) for four to five days until the desired INR has been reached. When the desired INR has been established, heparin can be abruptly discontinued. Although the INR is the test used to follow warfarin therapy, the drug may easily be monitored by PT, the laboratory test used to monitor heparin therapy. This is of minimal clinical significance.

Comment: Because most EPs rarely have to think much about warfarin other than the bleeding complications and maybe some drug interactions, most of us have forgotten the basics. I thought this was a good review. It is relatively self-explanatory, but I was amazed how much information is available to the general public. It’s possible that someone’s son or daughter, even without medical training, can know more about warfarin than you do when he brings his parent to the ED for warfarin therapy.

Speaking of patient information issues, FDA regulation 21CFR208 requires a “medication guide” to be provided with each prescription for products that the FDA has determined poses a serious public health concern. Warfarin is such a drug. The sagacious clinician should note the five in-depth pages of information patients now receive with their Coumadin prescriptions. It even tells the patient about cranberry juice interaction and the purple toe syndrome!

InFocus

WARFARIN INFORMATION FROM THE FDA

Warning: Bleeding Risk

Warfarin sodium can cause major or fatal bleeding. Bleeding is more likely to occur during the starting period and with a higher dose (resulting in a higher INR). Risk factors for bleeding include high intensity of anticoagulation (INR >4.0), age >65, highly variable INRs, history of gastrointestinal bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, malignancy, trauma, renal insufficiency, concomitant drugs (see PRECAUTIONS), and long duration of warfarin therapy. Regular monitoring of INR should be performed on all treated patients. The higher the dose who may benefit from more frequent INR monitoring, careful dose adjustment to desired INR, and a shorter duration of therapy. Patients should be instructed about prevention measures to minimize risk of bleeding and to report immediately to physicians signs and symptoms of bleeding (see PRECAUTIONS: Information for Patients).

Precautions: Drug-Drug and Drug- Disease Interactions

Numerous factors, alone or in combination, including changes in diet and medications, including botanicals, may influence the response of the patient to anticoagulants. It is generally good practice to monitor the patient’s response with additional PT/INR determinations in the period immediately after discharge from the hospital, and whenever other medications, including botanicals, are initiated, discontinued or taken irregularly. Drugs may interact with Coumadin through pharmacodynamic or pharmacokinetic mechanisms. Pharmacodynamic mechanisms for drug interactions with Coumadin are synergism (impaired hemostasis, reduced clotting factor synthesis), competitive antagonism (vitamin K), and altered physiologic control loop for vitamin K metabolism (hereditary resistance). Pharmacokinetic mechanisms for drug interactions with Coumadin are mainly enzyme induction, enzyme inhibition, and reduced plasma protein binding. It is important to note that some drugs may interact by more than one mechanism.

A test that measures thrombin generation can help determine whether patients who have experienced a venous blood clot are at low risk for a recurring blood clot, according to a study published in the July issue of the Journal of the American Medical Association.

A third of patients with venous thromboembolism (VTE) who discontinued anti-coagulant treatment experienced a recurrence of VTE within the next five to eight years. The case-fatality rate of recurrence was around five percent. As a result, identification of patients who might benefit from indefinite anticoagulant treatment is now one of the leading goals in thrombosis research. Assessing the risk of recurrence in an individual patient is complex because of the large number of risk factors, so a test that would detect multifactorial thrombophilia could help determine the overall risk of recurrent VTE.

Gregor Hron, MD, of the Medical University in Vienna, Austria, and colleagues conducted a study between July 1992 and July 2005 patients with VTE could be stratified into high- and low-risk categories for recurrent VTE by measuring thrombin generation. The study included 914 patients with first spontaneous VTE who were followed for an average of 47 months after discontinuation of vitamin K antagonists therapy. Thrombin generation was measured by a commercially available test.

In the study, VTE recurred in 100 patients (11%). Patients without recurrent VTE had lower thrombin than patients with recurrence. Patients with a first spontaneous VTE and peak thrombin generation of less than 400 nM after discontinuation of vitamin K antagonists had a low risk of recurrence.

According to Kaplan-Meier analysis, the chance of recurrent VTE in these patients was only as low as 4% after four years. Those with peak thrombin generation less than 400 nM had an almost 60 percent lower risk of recurrence compared with patients who had higher levels. Patients with low peak thrombin generation represented two-thirds of the total patient population. The study suggested that the test was able to identify patients in whom the long-term risk of recurrent VTE is almost negligible.
even though they are interested only in the INR. It’s time to stop this wasteful and time-consuming practice.

I am amazed how quickly the INR can change, often without obvious reasons. Usually one can ferret out the cause, but it’s not uncommon to see a bleeding patient with a markedly elevated INR when it was normal a week or two before. In one study of warfarin-induced hemorrhage, the mean INR at the time of the event was 6.0, but the mean INR at the last prior measurement, an average of 12 days before the bleeding event, was only 3.0. To me the implications are obvious. An INR should be obtained for every patient on warfarin in the ED for any event that could be even remotely related to coagulopathy or thrombosis. Back pain may be a spontaneous retroperitoneal hemorrhage, groin pain could be a clot in the femoral vein, and a mild headache could be a sign of intracerebral hemorrhage. I check an INR even if the patient swears it was fine when it was checked in the doctor’s office the week before. It would take only a few days for this test to be markedly out of whack.

The desired INR ranges from 2.0 to 3.0 for venous thromboembolism and slightly higher in patients with mechanical heart valves. It’s probably best to check with the primary physician or someone more versed in warfarin use before mucking around with the patient’s warfarin dose if it happens to be subtherapeutic. We all know what to do with a hypocoagulable patient (the topic of a future column).

As noted, warfarin is the chemical nomenclature, and Coumadin is a brand name. The INR should be monitored more frequently when one substitutes various manufacturers’ formulations of warfarin. There may be some change in drug availability, so a change in prescription plan, using a different pharmacy, or substituting generic for brand name is not without potential problems.

A future column will discuss drug-drug interactions, but it’s important to know that herbal preparations and OTC medications can affect INR. Most patients don’t think herbal medicines are of any great significance, and most clinicians don’t think a short course of antibiotics can alter a stable anticoagulated state, but they both can. The risk of overcoagulation is increased with common antibiotics such as amoxicillin, clarithromycin, and trimethoprim-sulfamethoxazole, often within the first three days of antibiotic use.

A plethora of patient characteristics are associated with an increased risk of bleeding following the use of warfarin. Increased age, usually over 60, is commonly quoted as an independent risk factor for exaggerated drug response. The propensity of old folks to fall has rendered many of them as not ideal candidates for warfarin. Other risk factors include alcoholism, being female, dia-

betes, and just about every disease. Of course, the concomitant use of aspirin or an NSAID is a universal prohibition.

I have never seen skin necrosis from warfarin, but it has been reported in some patients within the first few days of initiating large loading doses of warfarin. The lesions occur on the extremities, breasts, or trunk, and are actually due to fibrin thrombosis in the cutaneous vessels, rather than just a bruise. I could see how the two could be confused. The skin necrosis is thought to be mediated by the rapid reduction of protein-C levels during the first day of therapy, producing the previously described transient hypercoagulable state.

Finally, the origin of the word warfarin is of historical interest. Many years ago it was noted that cows that ate spoiled sweet clover tended to have bleeding episodes. The substance in the sweet clover was called coumarin. It was investigated by the Wisconsin Alumni Research Foundation (WARF). When you combine the Wisconsin group (WARF) with the compound coumarin, the name “warfarin” emerges. It’s great trivia for your next cocktail party and a good way to stump your internal medicine colleagues.

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**CME Participation Instructions**

To earn CME credit, you must read the article in *Emergency Medicine News*, and complete the quiz, answering at least 80 percent of the questions correctly. Mail the completed quiz with your check for $10 payable to Lippincott Continuing Medical Education Institute, Inc., 770 Township Line Road, Suite 300, Yardley, PA 19067. Only the first entry will be considered for credit and must be received by Lippincott Continuing Medical Education Institute, Inc. by January 30, 2008. Acknowledgment will be sent to you within six to eight weeks of participation.

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**January 2007**

**Questions:**

1. Warfarin is a proprietary name, and Coumadin is a brand name.
   - [ ] True  [ ] False

2. Warfarin inhibits Factors II, VII, IX, and X.
   - [ ] True  [ ] False

3. Warfarin inhibits the production of Protein C, causing an increased propensity for clotting before other clotting factors are fully affected.
   - [ ] True  [ ] False

4. Diet and antibiotics are of no clinical consequence in patients on warfarin.
   - [ ] True  [ ] False

5. When immediate anticoagulation is required for thrombosis, heparin and warfarin should be started simultaneously because initial warfarin therapy may produce a mild transient hypercoagulable state.
   - [ ] True  [ ] False

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1. Did the content of this activity meet the stated learning objectives?
   - [ ] Yes  [ ] No

2. On a scale of 1 to 5, with 5 being the highest, how do you rank the overall quality of this educational activity?
   - [ ] 5  [ ] 4  [ ] 3  [ ] 2  [ ] 1

3. As a result of meeting the learning objectives of this educational activity, will you be changing your practice behavior in a manner that improves your patient care? If yes, please explain.
   - [ ] Yes  [ ] No

4. Did you perceive any evidence of bias for or against any commercial products? If yes, please explain.
   - [ ] Yes  [ ] No

5. How long did it take you to complete this CME activity? _______ hour(s) _______ minutes

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