

Bleeding Risk

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The Case

A frail 78-year-old woman fell at home and fractured her left hip. Her past medical history included atrial fibrillation, hypertension, coronary artery disease, and stroke. The surgical repair and post-operative course were uneventful. The patient was discharged to a skilled nursing facility (SNF) for physical therapy on low-molecular-weight heparin, with a plan to initiate warfarin once it became clear that she was not at high risk for falls.

Two weeks into her admission at the SNF, the patient's physician began warfarin therapy at 5 mg daily. An INR level taken 3 days later was 1.5. Heparin was discontinued and warfarin was increased to 6 mg daily. An INR level was not ordered to be drawn for 7 days, at which time it was at a critical level of 20 (therapeutic range 2-3). The physician discontinued warfarin, but no other therapy was administered to reverse the anticoagulant effect. A repeat INR 3 days later was 12. A one time order for 10 mg of Vitamin K intramuscularly (IM) was administered. A repeat INR was ordered 2 days later, at which time it was 4.4—elevated but no longer critical. Two days after that, the INR was subtherapeutic at 1.4. At that point, the physician reinitiated warfarin at the original dosage of 5 mg daily. The INR did not become therapeutic for another 12 days, presumably because of the Vitamin K effect.

The Commentary

Warfarin is a highly effective, widely implemented, and well-proven intervention that markedly reduces the risk of both first and recurrent arterial and venous thrombosis. However, warfarin has a narrow therapeutic window and highly variable pharmacokinetics, both between individuals and within an individual over time. The fact that warfarin has variable pharmacokinetics has led to the development of a widespread infrastructure for its monitoring. Unlike other medications, the anticoagulant effect of warfarin can be routinely and reliably determined within hours in most hospital and outpatient laboratories.

The principal complication of warfarin therapy is hemorrhage. Although hemorrhage can occur in any patient receiving warfarin, the risk is magnified when the anticoagulant effect exceeds the usual therapeutic interval. Increasing the international normalized ratio (INR) by one point approximately doubles the risk of

bleeding.(1) Unexpected excessive prolongation of the INR is a common clinical problem; about 1 in 6 INR values will exceed the desired range. The risk of major bleeding is about 5% in the 2 weeks after patients present with an INR of more than 6.0 if they are treated with warfarin withdrawal alone.(1-3)

Monitoring the INR by experienced professionals reduces the risk of excessive (or inadequate) anticoagulation with the associated risks of bleeding (or thrombosis).(4) Thus, numerous studies have suggested that monitoring of oral anticoagulants in dedicated thrombosis clinics, using intelligent computer programs or patient self-monitoring with point-of-care INR testing, increases the time in the therapeutic range and reduces out-of-range INR values, the need for blood tests, and the costs and inconvenience of warfarin therapy.(4,5) In the hospital setting, where supervision of warfarin therapy is likely to be required regularly, development of a warfarin dosing algorithm for initial therapy and the use of either experienced staff or a computerized dosing system will likely reduce the risk of out-of-range INR values with their associated complications. These systems are also likely to detect changes in the patient's clinical condition or medication regimen that might increase the risk of out-of-range INR values (Table).

Medication errors specific to oral anticoagulants generally occur either due to inadequate monitoring, co-administration of medications that interact with warfarin, or inadequate treatment of excessively prolonged INR values. However, despite the number of patients who receive warfarin, and the frequency of excessively prolonged INR values, there has been little research into the frequency, clinical implications and costs of inappropriate warfarin dosing. However, several studies have recently been published which help to guide the management of patients with warfarin-associated coagulopathy.

A number of warfarin dosing algorithms have been developed.(6,7) These algorithms guide the frequency of INR determinations and the warfarin dose recommended based on the INR. For inpatients, INR determinations can be performed daily in the first days of warfarin therapy. For outpatients, less frequent monitoring can be performed; however, monitoring should occur at least biweekly during the early phase of therapy. Once a stable dosage of warfarin is achieved, the frequency of INR monitoring can be reduced to weekly for a period of 2 to 3 weeks, then monthly. If medications or diet are changed, increased monitoring of the INR is required.(8)

When patients present with an increased INR, the first priority is to determine if they are bleeding. Patients with major or life-threatening bleeding should receive parenteral vitamin K and coagulation factors; treatment of such patients is beyond the scope of this review, but has been reviewed in detail elsewhere.(9) For non-bleeding patients, two options are available: simple withdrawal of warfarin or administration of low-dose oral vitamin K.(10,11) Although the former strategy remains the standard of practice, it is likely associated with potentially avoidable major hemorrhage or death.(1) Therefore, the use of low-dose oral vitamin K is generally best in these situations. Administration of 1 mg of oral vitamin K reliably reduces INR values of 4.5 to 10.0 into the therapeutic range within 24 hours.(10) Although not studied, use of somewhat higher doses (eg, 2 mg to 2.5 mg orally) is likely effective in patients with higher INR values. Small doses of vitamin K have not been reported to produce "warfarin resistance" or to cause prolonged subtherapeutic INR values (both concerns have been raised in the past as reasons to avoid oral vitamin K). Subcutaneous vitamin K is less effective than oral, and its use cannot be recommended except in patients who cannot take oral medications.(12) Alternately, 0.5 mg of vitamin K intravenously reliably reduces markedly prolonged INR values into the therapeutic range within 24 hours.(13) The risk of anaphylaxis with

intravenous vitamin K has never been quantified, but appears to be very low. In all patients, the INR should be rechecked on the following day to ensure that it has fallen, which did not occur in this case.

This case illustrates a number of important issues. Warfarin is indicated in this case because of the atrial fibrillation; it also reduces the risk of DVT after orthopedic surgery when used after hospital discharge. The initial warfarin dosage was appropriate; however, it is worth keeping in mind that post-operative patients often require smaller dosages of warfarin than patients who have not had recent surgery.⁽¹⁴⁾ Thus using a smaller initial dosage of warfarin (eg, 3 mg) would have likely also been effective. The initial INR on day 3 is also appropriate. It is likely that continuing the warfarin at 5 mg per day would have resulted in a therapeutic INR. Although increasing the dosage is not unreasonable, the INR should have been monitored within 72 hours of the change. Some nursing facilities have routine bloodwork scheduled only weekly. For patients initiating warfarin, bloodwork will be required more often, and thus alternate arrangements are required.

When the INR is 20, most physicians would be uncomfortable simply withholding warfarin; administration of vitamin K is probably indicated in this circumstance.⁽⁴⁾ However, the dose of vitamin K (10 mg) was excessive in this case, and the route (intramuscular) was both unneeded (oral vitamin K being effective) and potentially dangerous (given the coagulopathy). The poor response of the INR to this large dose of vitamin K illustrates the relative ineffectiveness of vitamin K given by this route. If it had been given orally, the INR would likely have reached the desired range within 24 to 48 hours. It is also likely that if the dosage of warfarin had originally been left at 5 mg, and the INR monitored more closely, this entire scenario could have been avoided.

Take-Home Points

- Oral warfarin is safe and effective in the treatment and prevention of many thromboembolic disorders, but it has a relatively narrow therapeutic window.
- The use of published standard dosing algorithms may increase the safety of initial warfarin dosing.
- In the early days of therapy, fail-safe plans should be in place for frequent INR monitoring. This frequency can be cut back once a stable INR is achieved.
- Warfarin over-dosage places patients at risk for bleeding, particularly when the INR is above 6.0.
- Patients with supra-therapeutic INRs and active hemorrhage should receive parenteral vitamin K and clotting factors. For patients with supra-therapeutic INRs who are not bleeding, low-dose oral vitamin K is generally more effective than simply holding the warfarin in promptly reducing the INR.

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Table

Table. Causes of Abrupt Change in INR*

Causes of Increased INR	Examples
Reduced vitamin K availability	Use of antibiotics; unusual diets
Drug interactions	Drugs that inhibit metabolism of warfarin (eg, sulfonamides, metronidazole, isoniazid, amiodarone)
Toxins	Alcohol use
Overdosage	Inappropriate pill strength dispensed; intentional overdosage

Causes of Decreased INR	Examples
Enhanced vitamin K intake	Increased green leafy vegetables in diet
Drug interactions	Drugs that enhance clearance of warfarin or interfere with absorption (eg, rifampin, nafcillin, sucralfate)
Underdosage	Poor compliance

* These lists are not intended to be comprehensive; rather they should be used as a guide to the investigation of patients with unexpected changes in their warfarin requirements.

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