WARFARIN TOXICITY MANAGEMENT

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ABSTRACT
Warfarin also known as coumadin belongs to a class of medications known as anticoagulation. It is used to prevent blood clots in certain medical conditions. Warfarin works by preventing platelets from sticking together to form blood clots.

Warfarin can cause serious bleeding especially when it is taken without proper monitoring. INR is supposed to be the best method for monitoring of warfarin. Management of warfarin toxicity is done by stoppage of warfarin initially and then administration of Vit-K, FFP, Factor Concentrate and Prothrombin complex concentrate.

INTRODUCTION
The coumarin derivative warfarin, which was licensed in the United States in 1954 as the first human anticoagulant,\(^1\) remains the most commonly used oral anticoagulant in North America and the United Kingdom.\(^2,3\) Warfarin exerts its anticoagulant effect by acting as a vitamin K antagonist and inhibiting the biosynthesis of vitamin K-dependent procoagulant factors II, VII, IX and X.\(^2,4,5\) The maximum dose effect occurs up to 48 hr after administration of a single dose and persists for the next 5 days.\(^6\)

Nonetheless, in 1995 the AHCPR reported that warfarin is greatly underutilized for stroke prevention. The AHCPR noted that physicians are reluctant to prescribe warfarin, in part because they are not familiar with techniques for administering the drug safely and fear that the drug will cause bleeding. Patients treated with warfarin do require close monitoring to avoid bleeding but it has been shown that the drug prevents 20 strokes for every bleeding episode that it causes.

Warfarin overdose results from the administration of inappropriately high doses, altered protein binding, decreased vitamin K intake, reduced synthesis or increased clearance of vitamin K-dependent clotting factors and the simultaneous use of other drugs (e.g. Erythromycin, fluconazole, amiodarone, propranolol, proxicam, and omeprazole) that compete with warfarin for protein binding.\(^8\)

Warfarin therapy is challenging because of substantial individual variations in dosage requirements that make over-anticoagulation common.\(^2,8\) In addition, because warfarin has a narrow therapeutic window, treatment frequently results in bleeding, sometimes major or life-threatening.\(^9\) Major bleeding, typically involving the gastrointestinal or urinary tracts or soft tissue, occurs in up to 6.5% of anticoagulated patients per year.\(^10\) The incidence of fatal bleeding, primarily Intracranial hemorrhage (ICH), is approximately 1% annually.\(^10-14\) The risk of hemorrhage increases with the intensity of warfarin anticoagulation; the variable most consistently associated with bleeding risk is elevation of the international normalized ratio(INR), a standardized prothrombin time.\(^5,3\) For most warfarin indications, the target maintenance INR is 2.0 to 3.\(^16,15\) However, the risk of bleeding is heightened even at low anticoagulation intensity (INR < 2.0),\(^17\) and increases exponentially when the INR exceeds 5.0.\(^12,13\)

The goal of urgent warfarin reversal is to elevate or replace vitamin K-dependent clotting factors.\(^16\) The method used is determined by the INR and the clinical seriousness of the bleeding event.\(^2,16\) Oral doses
of vitamin K achieve partial reversal within 24 hr. whereas intravenous (IV) administration reverses anticoagulation within 4-8 hr. High doses will not further shorten the time to anticoagulation reversal but may lower INR more than is necessary and cause warfarin resistance that persists for up to 1 week. There is general consensus that major or life-threatening bleeding requires rapid and complete warfarin reversal. Fresh frozen plasma (FFP) is widely available and provides fast, partial reversal of the coagulopathy through the replacement of exogenous factors II, VII, IX, and X (F II, F III. FIX and FX). FFP is considered the general standard of care in the United States, and although the optimal dose has not been established, FFP is most often administered in a dose of 15 ml/kg. Volume overload may make it difficult to administer an adequate FFP dose, particularly since patients often have compromised cardiovascular systems. FFP contains isoheamagglutinins and must be blood group specific. It also must be thawed before use, which can delay treatment, and infection transmission is a potential risk. In patients with very dependent factors, replacement of hemostatic levels of these factors cannot be achieved with tolerable doses of FFP. Furthermore, the administration of FFP in recommended doses is often insufficient to normalize FIX levels.

**MANAGEMENT OF PATIENTS WITH WARFARIN TOXICITY**

There is a close relation between the INR and risk of bleeding. The risk of bleeding increases when the INR exceeds 4, and the risk rises sharply with values > 5. Three approaches can be taken to lower an elevated INR. The first step is to stop warfarin; the second is to administer vitamin K1; and the third and most rapidly effective measure is to infuse fresh plasma or prothrombin concentrate. The choice of approach is based largely on clinical judgement because no randomized trials have compared these strategies with clinical end points. After warfarin is interrupted, the INR falls over several days (an INR between 2.0 and 3.0 falls to the normal range 4 to 5 days after warfarin is stopped). In contrast, the INR declines substantially within 24 hours after treatment with vitamin K1.

Even when the INR is excessively prolonged, the absolute daily risk of bleeding is low, leading many physicians to manage patients with INR levels as high as 5 to 10 by stopping warfarin expectantly, unless the patient is at intrinsically high risk of bleeding or bleeding has already developed. Ideally, vitamin K1 should be administered in a dose that will quickly lower the INR into a safe but not subtherapeutic range without causing resistance once warfarin is reinstated or exposing the patient to the risk of anaphylaxis. Though effective, high doses of Vitamin K1 (e.g. 10 mg) may lower the INR more than necessary and lead to warfarin resistance for up to a week.

Vitamin K1 can be administered intravenously, subcutaneously, or orally. Intravenous injection produces a rapid response but may be associated with anaphylactic reactions, and there is no proof that this rare but serious complication can be avoided by using low doses. The response to subcutaneous vitamin K1 is unpredictable and sometimes delayed. In contrast, oral administration is predictably effective and has the advantages of convenience and safety over parenteral routes. In patients with excessively prolonged INR values, vitamin K1, 1 mg to 2.5 mg orally, more rapidly lowers the INR to < 5 within 24 hours than simply withholding warfarin. In a prospective study of 62 warfarin-treated patients with INR values between 4 and 10, warfarin was omitted, and vitamin K1, 1 mg was administered orally. After 24 hours, the INR was lower in 95%, <4 in 85% and < 1.9 in 35%. None displayed resistance when warfarin was resumed. These observations indicate that oral vitamin K1 in low doses effectively reduced the INR in patients treated with warfarin. Oral vitamin K1 1.0 to 2.5 mg, is sufficient when the INR is between 4 and 10, but larger doses (5 mg) are required when the INR is > 10.

Oral vitamin K1 is the treatment of choice unless very rapid reversal of anticoagulation is critical, when vitamin K1 can be administered by slow intravenous infusion (5 to 10 mg over 30 minutes). In 2001, the American College of Chest Physicians published the following recommendations for managing patients on coumarin anticoagulations who need their INRs lowered because of either actual or potential bleeding.

### 1. When the INR is above the therapeutic range but <5, the patient has not developed clinically significant bleeding, and rapid reversal is not required for surgical intervention, the dose of a warfarin can be reduced or the next dose omitted and resumed (at a lower dose) when the INR approaches the desired range.

### 2. If the INR is between 5 and 9 and the patient is not bleeding and has no risk factors that predispose to bleeding, the next 1 to 2 doses of warfarin can be omitted and warfarin reinstated at a lower dose when the INR falls into the therapeutic range. Alternatively, the next dose of warfarin may be omitted and vitamin K1 (1 to 2.5 mg) given orally. This approach should be used if the patient is at increased risk of bleeding.

### 3. When more rapid reversal is required to allow urgent surgery or dental extraction, vitamin K1 can be given orally in a dose of 2 to 5 mg anticipatory reduction of the INR within 24 hours. An additional dose of 1 to 2 mg vitamin K can be given if the INR remains high after 24 hours.

### 4. If the INR is > 9 but clinically significant bleeding has not occurred, Vitamin K1, 3 to 5 mg, should be given orally, anticipating that the INR will fall within 24 to 48
hours. The INR should be monitored closely and vitamin K repeated as necessary.

1. When rapid reversal of anticoagulation is required because of serious bleeding or major warfarin overdose (e.g. INR >20), vitamin K1 should be given by slow intravenous infusion in a dose of 10 mg, supplemented with transfusion of fresh plasma or prothrombin complex concentrate, according to the urgency of the situation. It may be necessary to give additional doses of vitamin K1 every 12 hours.

2. In cases of life-threatening bleeding or serious warfarin overdose, Prothrombin complex concentrate replacement therapy is indicated, Supplemented with 10 mg of vitamin K1 by slow intravenous infusion; This can be repeated, according to the INR,. If warfarin is to be resumed after administration of high doses of vitamin K, then heparin can be given until the effects of vitamin K have been reversed and the patient again becomes responsive to warfarin.

3. Early PCC products, including those currently available in the United States, contain factors II, IX and X. Newer products include factor VII. Some contain protein C and protein Z, antithrombin II, and/or heparin. Across 4-factor products however, there appears to be rapid reversal of coagulopathy within 10-30 minutes.29

4. Recombinant factor VIIa has been shown to correct INR within hours.30,31,32 The potential benefits of rFVIIa or PCC over FFP include rapid Administration (because rFVIIa and PCC do not have to be thawed), smaller infusion volumes, and decreased risk of transfusion-associated adverse reactions. Studies have shown improvement only of secondary end points, such as intracranial hematoma size, total volume of blood products, and time to operative intervention.31-34

An algorithm for the management of bleeding and excessive anticoagulation was included in the 1998 anticoagulation guidelines:23

- If 3.0 < INR < 6.0 (target INR 2.5) then :
  - reduce warfarin dose/stop warfarin
  - restart warfarin when INR <5.0

- If 4.0 < INR < 6.0 (target INR 3.5) :
  - reduce warfarin/stop warfarin
  - restart warfarin when INR < 5.0

- If 6.0 < INR < 8.0 and no bleeding or minor bleeding then :
  - stop warfarin
  - restart when INR < 5.0

- If INR > 8.0 and no bleeding or minor bleeding then :
  - stop warfarin
  - restart warfarin when INR < 5.0

  Of oral vitamin K

If major bleeding then :
- stop warfarin

Managing bleeding and excessive anticoagulation

- reversal of anticoagulation with vitamin K is achieved more rapidly with intravenous administration than oral administration

- in the original guideline an option of 5 mg of Vitamin K orally or intravenously was recommended for patients with major bleeding, in addition to factor replacement therapy with either a factor concentrate or fresh frozen plasma (FFP). The updated guideline now considers that, in patients with major bleeding, reversal with intravenous vitamin K is preferable. A dose of either 5 or 10 mg is recommended. Complete and rapid reversal of over-anticoagulation is more readily achieved with a factor concentrate than with FFP.

Intravenous vitamin K should be given if reversal is to be sustained. The guideline recommends that reversal of anticoagulation in patients with major bleeding requires administration of a factor concentrate in preference to FFP, when this is available and administration of intravenous rather than Oral Vitamin K and administration of intravenous rather than oral vitamin K.28

Unexpected bleeding at therapeutic levels :
- Investigate for possible cause e.g. alimentary or renal disease.

SUMMARY

Judicious use of warfarin in treating and preventing blood clots, especially in deep vein thrombosis and pulmonary thromboembolism should be the first cautious steps to keep warfarin toxicity at a distance. INR is by for the best method for monitoring warfarin toxicity. The management should be initiated promptly. Stoppage of warfarin with regular check up of INR is the cornerstone of treatment.

Once bleeding starts and INR is very high, Vit K, FFP, Factor concentrate and PCC have shown to be very effective.

REFERENCES


