SUNNYBROOK & WOMEN'S

P&T Bulletin

A Publication of the Pharmacy & Therapeutics Committee
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Number 30, October 2002 (***revised January 2006***)

REVERSAL OF WARFARIN OVER-ANTICOAGULATION: FOCUS ON VITAMIN K

The risk of hemorrhage is believed to rise sharply at INR values of 6.0 and above. Specific management of excessive anticoagulation during warfarin therapy depends on several factors, including the INR value, the risk for major bleeding, and the severity of bleeding if present (see table, reverse side).

WITHHOLDING WARFARIN

Withdrawal of warfarin results in a slow return of supratherapeutic INR values to the therapeutic range. In 562 patients with INR of 6.0 to 10.0, withholding 2 doses of warfarin resulted in INR values of < 4.0 in 67% of patients after 48 hours. Data from another series of patients with INR values of 5-8 indicates that 24 hours after stopping warfarin only 58% had an INR value < 5.0; at 48 hours, 84% of INRs were still > 3.0.

Complete reversal of anticoagulation (i.e., reduction of INR value to $\leq$ 1.2) among a group of patients with therapeutic INR values (mean 2.6, range 1.95 – 3.8) was achieved in only 10% of patients 3 days after withdrawal of warfarin, and in 80% after 5 days. Thus, administration of vitamin K is required when more prompt or complete reversal of anticoagulation is necessary.

USE OF VITAMIN K

Most patients with supratherapeutic INR values do not require vitamin K. Fewer than 4% of patients with an INR > 6 will develop major bleeding if no active intervention is instituted. Thus, the absolute daily risk of bleeding is low. Assessment of the individual patient's risk for clinically important bleeding is required to identify appropriate candidates for vitamin K administration. Patients with liver disease, alcoholism, uncontrolled hypertension, recent stroke, or history of GI bleed warrant special consideration regarding bleeding risk. Active cancer, congestive heart failure, low warfarin dose requirement, and concomitant use of warfarin-potentiating drugs are factors that have been shown to be associated with a slower rate of decline of INR value following withdrawal of warfarin.

Vitamin K should be given in a dose that is sufficient to quickly reduce the INR value into a safe range. However, unless there is significant bleeding, the vitamin K dose should not be so large as to result in a subtherapeutic INR. In the absence of significant bleeding, high doses of vitamin K (e.g., 5-10 mg) should be avoided since they may induce a state of warfarin resistance. Recent data confirm the efficacy of vitamin K in doses < 5 mg (e.g., 1 to 2.5 mg) for correction of supratherapeutic INR values in the absence of significant bleeding. Vitamin K is available in two strengths of injectable solution: 10 mg per 1 mL ampoule and 1 mg per 0.5 mL ampoule. At S&W, only the 10 mg per 1 mL amp is widely distributed in an effort to reduce the potential for administration errors.

Oral administration of vitamin K has emerged as the preferred route for non-emergent reversal of warfarin-induced excessive anticoagulation in the absence of significant bleeding. Low doses in the range of 1 mg to 2.5 mg are effective and less likely to induce warfarin resistance. A substantial reduction of INR value is usually evident within 8-24 hours. Since there is no oral tablet marketed in Canada, the parenteral product must be used for oral administration. The required volume of injectable solution (e.g., 0.1 – 0.25 mL for doses of 1 – 2.5 mg) is withdrawn from the ampoule and added to a small volume of a palatable beverage for the patient to drink.

Intravenous infusion is preferred in situations when more rapid reversal of anticoagulation is required. A significant effect on the INR is usually evident within 4-6 hours after IV administration of vitamin K. The required dose (usually 5-10 mg) is added to 50 mL of D5W and infused over 15-30 minutes.

Subcutaneous (SC) injection of vitamin K has been widely used; however, the SC route of administration is not efficient for reversal of excessive anticoagulation. In a group of asymptomatic patients with supratherapeutic INR values (4.5 - 10), oral vitamin K 1 mg reduced the INR more rapidly and more reliably than 1 mg injected SC. Therefore, **SC injection of vitamin K is not recommended**.

Intramuscular (IM) injection of vitamin K should never be used. Efficacy data are lacking, and patients with high INR values are at risk of hematoma formation at the injection site.

MANAGEMENT OF WARFARIN OVER-ANTICOAGULATION

Bleeding Status	INR	Recommended Management
No Bleeding	**Above therapeutic but < 5**	• Investigate cause of ↑ INR: infection, heart failure, dosing error • Consider omitting one dose of warfarin • Monitor INR to assess response (e.g., in 1-2 weeks) • Resume warfarin at lower dose • If INR only minimally above therapeutic range, dosage reduction may not be required
	5 – 10	• Investigate cause of ↑ INR: infection, heart failure, dosing error • Omit the next 1-2 doses of warfarin • Monitor INR to assess response (e.g., in 3-5 days) • Resume warfarin at a lower dose when INR approaches the therapeutic level • Alternatively, omit 1 dose and give oral vitamin K 1 to 2.5 mg
	> 10	• Investigate cause of ↑ INR: infection, heart failure, dosing error • Hold warfarin • Give oral vitamin K 2.5 to 5 mg (should reduce INR in 24-48 hours) • Monitor INR to assess response (e.g., in 2 days) • Consider additional vitamin K as necessary • Resume warfarin at a lower dose when INR approaches the therapeutic level
Minor Bleeding	**Any Elevation ***	• Investigate cause of ↑ INR: infection, heart failure, dosing error • Hold warfarin if INR > 3.0 • Give oral vitamin K 1 to 2.5 mg if INR > 5.0 • Reassess symptoms and INR until episode resolves
Serious or Life-Threatening Bleeding	**Any Elevation ***	• Investigate cause of ↑ INR: infection, heart failure, dosing error • Hold warfarin • Give IV vitamin K 10 mg in D5W 50 mL over 15-30 minutes • Give frozen plasma 15 mL per kg rounded up to the nearest 250 mL • Additional vitamin K can be repeated every 12 hours if necessary

* If patient is bleeding, it is appropriate to reverse the anticoagulant effect of warfarin even if the INR is not supratherapeutic

COMPLETE REVERSAL OF ANTICOAGULATION: NORMALIZATION OF THE INR VALUE

Patients who need prompt, complete reversal of anticoagulation (e.g., return of the INR to < 1.5 within 2-8 hours) should receive **IV** vitamin K in a dose of 2.5 to 10 mg. Frozen plasma should be considered as appropriate (benefit persists for only 6 hours). Patients receiving warfarin who are scheduled for an elective major surgical procedure should have the warfarin discontinued 3-4 days before the procedure. If the INR is still > 2 on the day prior to the procedure, vitamin K may be given orally in a dose of 1 to 2.5 mg.