Reversal of Warfarin-induced Coagulopathy: Review of Treatment Options

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Warfarin is a mainstay of the treatment of a variety of common conditions requiring anticoagulation, including deep venous thrombosis, pulmonary embolism, and atrial fibrillation. Treatment with warfarin requires careful monitoring and dose adjustments because of a narrow therapeutic index. A small window of optimal anticoagulation exists between the lower level of anticoagulation that could still result in clot formation and a higher level of anticoagulation that increases the risk of hemorrhage.

Many factors determine the maintenance dose of warfarin prescribed for a particular patient. The most common factors include the patient's age, diet, presence of hepatic disease, and concomitant medications. The international normalized ratio (INR) is used to monitor warfarin's effect on coagulation in the body. The INR is calculated by measuring the activity of circulating clotting factors. Supra-therapeutic levels of anticoagulation may occur when patients alter how they take their medication or change their diet, start new medications, or do not have regular follow-up checkups of their INR. In many cases, a patient with a supra-therapeutic INR will require reversal of anticoagulation to prevent, slow, or stop an active hemorrhage. Modalities such as vitamin K, fresh frozen plasma (FFP), recombinant factor VIIa, and prothrombin concentrate complexes (PCCs) may be used to attempt to correct this drug-induced coagulopathy.

The decision to reverse anticoagulation for a patient and the treatment regimen chosen to do so varies greatly with the clinical condition of the patient, more so than the actual INR value. For example, an asymptomatic patient with an INR of 5 does not require any intervention and could be counseled to hold subsequent doses and follow up with his or her outpatient clinic. In contrast, a patient with an intracerebral hemorrhage (ICH) who has an INR of 5 would likely need the full complement of available reversal agents. Clinical practice guidelines for reversal of warfarin-induced coagulopathy are published by the American College of Chest Physicians and include recommendations for treatment of a variety of clinical conditions and their associated INR levels.[1] To better understand the treatment options for warfarin-induced coagulopathy, it is important to have a basic foundation in how warfarin affects the body and how outside factors affect warfarin's potency.

Understanding Warfarin

Warfarin acts as an anticoagulant by decreasing the synthesis of vitamin K–dependent clotting factors produced by the liver. Vitamin K is critical in the formation of some these factors, and warfarin acts to decrease the availability of vitamin K for this process. This process results in production of clotting factors with a reduced activity, thus prolonging the INR. These clotting factors include factors II, VII, IX, X, and proteins C and S.

Warfarin is metabolized by the liver and is subject to a variety of factors that may increase or decrease the rate of metabolism. These factors include age, the presence of hepatic disease, medications, and diet. Warfarin's normal half-life is 20 to 60 hours, meaning that the drug continues to affect coagulation long after the last dose is taken. Warfarin is metabolized via the cytochrome P450 system, which is influenced by a variety of medications including antifungal agents (eg, fluconazole), antibiotics (eg, levofloxacin and metronidazole), and amiodarone, to name a few (Table 1). The addition of these medications often causes a subsequent increase or decrease in the drug levels of warfarin in the body and thus a corresponding change in the INR. In addition, diet plays a large role in the effectiveness of warfarin. Vitamin K, the target of warfarin's mechanism, is found in many food items, and when ingested, it pro-

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TABLE 1
Common medications associated with increased international normalized ratio in patients taking warfarin

- Amiodarone
- Antibiotics
  - Sulfamethoxazole/ trimethoprim (Bactrim)
  - Ciprofloxacin (Cipro)
  - Levofloxacin (Levaquin)
  - Cimetidine (Tagamet)
  - Erythromycin
  - Metronidazole
- Antifungal agents
  - Fluconazole (Diflucan)
  - Ketoconazole

vides more substrate for the warfarin to act upon, and a drop in INR may occur.

These influencing factors account for many of the ED visits related to warfarin anticoagulation. Patients often may notice bleeding from activities of daily living such as brushing or flossing. In addition, warfarin-induced coagulopathy accounts for many cases of ICH in persons who present to the emergency department. An emergency nurse familiar with warfarin's properties will be better prepared to target effective reversal therapies.

The decision to reverse warfarin-induced coagulopathy depends on many factors but generally is directed by the clinical condition of the patient. Reversal treatments include vitamin K, FFP, recombinant factor VIIa, and PCCs. These treatment choices have a variety of properties that define their usefulness.

Vitamin K

Vitamin K is the cornerstone of definitive warfarin reversal. Because vitamin K is warfarin's main target in its mechanism of action, by providing increased levels of vitamin K, the liver is able to again produce normal clotting factors. In combination with the lasting effect of warfarin and the time required to synthesize a significant amount of new clotting factors, the full effect of administering vitamin K is delayed. The inherent limitation of administering vitamin K is that approximately 24 hours must elapse before a significant effect occurs.

The recommended dose and route of vitamin K vary based the clinical condition of the patient and the INR in some cases. Single doses commonly range from 1 to 10 mg. It is important to tailor the required amount of vitamin K needed to treat the patient. Administering excessive dosages of vitamin K may cause the INR to drop well below the target level, and warfarin resistance can occur. Vitamin K–induced warfarin resistance may last a week or more and causes difficulty in reaching a target INR when administration of warfarin is restarted.

When warfarin is reversed in a non-emergent situation, vitamin K should be administered orally. Subcutaneous administration is associated with delayed and erratic absorption and should not be used. Vitamin K carries a black box warning against use of intravenous, intramuscular, and subcutaneous administration unless the serious risk is justified. The intravenous administration of vitamin K is associated with anaphylactic reactions and may cause shock and cardiac or respiratory arrest. However, the intravenous route may be used in cases that warrant emergent reversal according to the American College of Chest Physicians.[1] These cases include serious and life-threatening bleeding, including intracranial hemorrhage. If intravenous administration is necessary, vitamin K should only be administered by slow intravenous infusion. Recommendations on exact dilutions vary, but many institutions dilute 10 mg vitamin K in 50 mL of sodium chloride 0.9% (normal saline solution) or dextrose 5% in water (D5W). Recommended administration times also vary and are between 15 minutes to 1 hour. Rapidly administering vitamin K provides no additional impact on warfarin-induced coagulopathy.[1]

Fresh Frozen Plasma

FFP is a blood product produced from the separation of the liquid portion of whole blood. FFP contains all coagulation factors. FFP is recommended for reversal of warfarin-induced coagulopathy regardless of INR when serious or life-threatening bleeding is present.[1] Warfarin acts to decrease the concentration of functional clotting factors in the body. FFP is administered in an attempt to augment the number of functional clotting factors to a higher level.

Dosage recommendations for FFP are largely empiric. The traditional dose of FFP is 10 to 15 mL/kg of patient body weight, although some sources recommended doses up to 20 mL/kg for life-threatening hemorrhages.[2] In general, 1 unit of FFP contains 175 to 250 mL of volume. The limitation with FFP therapy is the volume required to reverse a person's warfarin-induced coagulopathy; the average dose of FFP needed for an adult is about 4 units. In general, most patients taking warfarin have multiple disease states, and many have congestive heart failure. In administering FFP it is important to monitor for complications of such high volumes of infusions.[2]