Strategies for Reversal of Warfarin Following Acute Bleed

Authors: Brian W. Gilbert, PharmD, BCPS, BCCCP, Tessa Reynolds, PharmD, Joel B. Huffman, PharmD, and Katherine Hall, PharmD, BCPS, Wichita, KS
Section Editor: Allison A. Muller, PharmD, D.ABAT

CE Earn Up to 7.5 Hours. See page 338.

A patient with altered mental status presents via EMS after being found by family. She has a medical history significant for hypertension, diabetes, and atrial fibrillation for which she receives oral anticoagulation for stroke prevention. After the initial workup comes back negative, a computed tomographic scan of the brain is performed and the patient is found to have a large intraparenchymal hemorrhage that extends into the ventricles.

Oral anticoagulant–induced intracranial hemorrhage is associated with morbidity and mortality rates as high as 68%.[1] Rapid reversal of anticoagulants has been adopted as one of the standards of care for patients who experience life-threatening bleeds in the emergency department. Warfarin, which inhibits vitamin K–dependent clotting factors II, VII, IX, and X, is still one of the most widely prescribed oral anticoagulants.[2] Whereas some of the newer direct oral anticoagulants currently do not have widely available reversal options, warfarin has prothrombin complex concentrate (PCC), vitamin K (phytonadione), and fresh frozen plasma (FFP) as options for reversal.[3] Although a higher international normalized ratio (INR) places patients at higher risk for the development of spontaneous bleeds, the fact remains that a patient may experience a life-threatening bleed at any INR while taking warfarin. This review compares and contrasts some of the agents available for warfarin reversal.

Brian W. Gilbert is Emergency Medicine Clinical Pharmacy Specialist, Wesley Medical Center, Wichita, KS.

Tessa Reynolds is PGY-2 Critical Care Pharmacy Resident, Wesley Medical Center, Wichita, KS.

Joel B. Huffman is Emergency Medicine Clinical Pharmacy Specialist, Wesley Medical Center, Wichita, KS.

Katherine Hall is Surgical & Trauma Intensive Care Clinical Pharmacy Specialist, Wesley Medical Center, Wichita, KS.

For correspondence, write: Brian W. Gilbert, PharmD, BCPS, BCCCP, Wesley Medical Center, 550 N Hillside Ave, Wichita, KS 67214; E-mail: brian.gilbert.pharmd@gmail.com.

J Emerg Nurs 2019;45:327-8.
0099-1767

https://doi.org/10.1016/j.jen.2018.11.015

Vitamin K (Phytonadione)

Factors II, VII, IX, and X are all dependent on vitamin K for synthesis. Therefore, vitamin K for warfarin reversal is considered part of first-line treatment. It has a peak onset of action around 4 to 6 hours after IV administration, and if needed for emergent reversal, the IV formulation should be the only form considered. Oral and subcutaneous vitamin K formulations can have sporadic absorption, and intramuscular formulations have been known to cause hematoma expansion, as well as delayed onset of action for persons with supratherapeutic INRs.[4] Vitamin K given intravenously, in older undiluted formulations, has been associated with anaphylactic reactions. For this reason, it should be diluted with a minimum of 50 mL normal saline per 10 mg and infused over a minimum of 20 minutes. Because of its slower onset of action, if more immediate reversal is needed, vitamin K should be given as an adjunct to either FFP or PCC.

Prothrombin Complex Concentrate

PCC is a concentrated form of vitamin K–dependent clotting factors. PCC can be stratified by the number of vitamin K–dependent clotting factors in the formula and the presence or absence of active or inactive factors. Three-factor PCC (3PCC) contains clotting factors II, IX, and X, whereas 4-factor PCC (4PCC) contains the same factors plus factor VII. The formulation is considered to be activated if it contains VIIa and inactive if it contains VII. Current recommendations are to utilize a 4PCC rather than a 3PCC formulation for warfarin reversal because it has been shown to be more effective at reversing INR values.[2,4,5] With respect to activated 4PCC versus inactive, a paucity of data continues to hinder efforts to determine the true value of having VIIa within the formula, and further studies are needed to determine its exact role in warfarin reversal.

Some of the benefits of utilizing PCC is a fast onset of action, less administration volume, fewer adverse effects when compared with FFP, and faster INR reversal.[4] Traditionally, dosing has been based on weight and initial INR;

TABLE
Comparison of agents for warfarin reversal

Characteristic	Intravenous vitamin K[4,6]	PCC[2-4,6]	FFP[4,6]
Mechanism of action	Promotes liver synthesis of clotting factors	Provides concentrate vitamin K–dependent coagulation factors	Replaces human plasma proteins, including clotting factors
Effect time	Slow (4-6 h)	Fast (10 min)	Fast (10 min)
Half-life	12-24 h	6-8 h	1.5-2 d
Pros	Nonblood product; oral option available; less expensive	Does not require blood typing; fast onset of action; small volume administration	Fast onset of action; second line option if PCC is not available
Cons	Anaphylaxis with IV route (older undiluted formulations); delayed onset of action; peak effect may make reanticoagulation difficult	Expensive; data for activated PCC vs inactivated PCC is inconclusive; possible concern for thromboembolic events; possible rebound INR if used monotherapy	Requires blood typing; must be thawed prior to administration; large volume administration causing transfusion-related reactions

FFP = fresh frozen plasma; INR = internal normalized ratio; PCC = prothrombin complex concentrate.

however, recently data have been emerging on the utilization of fixed-dose or indication-based dosing regimens that have been endorsed as an option in the American College of Cardiology guidelines for reversal of oral anticoagulants.[6] For life-threatening bleeds, PCC must be given with vitamin K because PCC has a short half-life and rebound increases in INR can occur once PCC effects have worn off.

Fresh Frozen Plasma

FFP is a nonconcentrated blood product that contains all the coagulation factors found in human blood needed to reverse warfarin. Like PCC, it too has a relatively fast onset of action; however, it is associated with a much greater administration volume because each unit of FFP consists of approximately 250 mL.[4] A large volume of administration (2 to 4 L) often is needed to fully reverse warfarin activity, and more adverse effects are associated with FFP than with PCC, such as transfusion-related lung injury and transfusion-associated circulatory overload.[3] As with PCC, vitamin K should be administered concomitantly with FFP. Current guidelines recommend PCC over FFP for warfarin reversal based on data showing faster INR reversal and reduced adverse events compared with FFP.[6]

Conclusion

Although FFP, PCC, and vitamin K are not the only agents that have been evaluated in the management of patients who need emergent warfarin reversal, they are the mainstay of therapy and the most studied. The Table compares and contrasts some of the differences and pros/cons of utilization of each agent discussed in this review. Although each agent has advantages and disadvantages, other aspects of care cannot be overlooked, such as discontinuation of the offending agent, possible drug-drug interactions that could prolong the anticoagulant effect of warfarin, and mitigating safety hazards for patients who are prone to bleeding.

REFERENCES

1. Faine BA, Amendola J, Homan J, et al. Factors associated with availability of anticoagulation reversal agents in rural and community emergency departments. *Am J Health Syst Pharm*. 2018;75(2):72-77.
2. Scott R, Kersten B, Basior J, et al. Evaluation of fixed-dose four-factor prothrombin complex concentrate for emergent warfarin reversal in patients with intracranial hemorrhage. *J Emerg Med*. 2018;54(6):861-866.
3. Rowe AS, Dietrich SK, Phillips JW, et al. Activated prothrombin complex concentrate versus 4-factor prothrombin complex concentrate for vitamin K-antagonist reversal. *Crit Care Med*. 2018;46(6):943-948.
4. Thigpen JL, Limdi NA. Reversal of oral anticoagulation. *Pharmacotherapy*. 2013;33(11):1199-1213.
5. DeAngelo J, Jarrell D, Cosgrove R, et al. Comparison of 3-factor versus 4-factor prothrombin complex concentrate with regard to warfarin reversal, blood product use, and costs. *Am J Ther*. 2018;25(3):e326-e332.
6. Tomaselli GF, Mahaffey KW, Cuker A, et al. 2017 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology task force on expert consensus decision pathways. *J Am Coll Cardiol*. 2017;70(24):3042-3067.