What Is the Evidence for the Off-label Use of Recombinant Factor VIIa (rFVIIa) in the Acute Reversal of Warfarin?

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A 47-year-old man presents with hypovolemic shock. He takes warfarin as a result of a mechanical mitral valve insertion 5 years prior, his INR at presentation is 8.4 and emergent CT reveals a very large retroperitoneal hematoma. Despite aggressive fluid and transfusion support he continues hypotensive, requiring ionotrope support. You are asked if he should receive recombinant factor VIIa.

To examine current best evidence of the effect of recombinant factor VIIa (rFVIIa) on the reversal of warfarin-induced coagulopathy, we performed a comprehensive computerized literature search of the OVID database using the terms warfarin (MESH, no restrictions, 13764 hits), AND recombinant factor VIIa (MESH, including factor VII, factor VIIa, and recombinant FVIIa, 5928 hits), AND reversal (MESH, no restrictions, 39639 hits) OR correction (MESH, no restrictions, 72783 hits) between 1950 and week 2 May 2008. This strategy provided 22 hits. There were 4 additional studies gleaned from the reference list of 2 of the articles.[1-4] Twelve papers were excluded: 7 were review articles,[5-11] 3 described effects of clotting factor concentrates or vitamin K and not rFVIIa,[12-14] 1 compared the *in vitro* antifibrinolytic activity of prothrombin complex concentrates to rFVIIa,[15] and 1 was a case report of rFVIIa in a phenindione overdose.[16] Five case series, 5 case reports, 1 retrospective case-control, 1 retrospective chart review, and 1 database review were retrieved. There was also 1 study involving healthy volunteers that included a dose finding study followed by a randomized controlled trial.

The randomized double-blind placebo controlled trial was a pharmacokinetic-pharmacodynamic study of 28 healthy volunteers given acenocoumarol followed by rFVIIa (doses ranging from 5 to 320 μg/kg). The dose finding aspect of the study revealed that a single dose of 5 μg/kg normalized the INR for 12 hours and doses >120 μg/kg normalized the INR for 24 hours. The placebo had no effect on the INR.[2]

Eight of the retrieved reports involved patients experiencing warfarin-related central nervous system (CNS) bleeds. In one case series, rFVIIa was given to 7 patients with acute CNS bleeds with pretreatment INRs ranged from 1.7 to 6.6. Within 10 minutes of dosing at a range of 10 to 40 μg/kg, all INRs were less than 1.5. All but 1 patient had also received vitamin K and 3 had received fresh frozen plasma (FFP).[17] Another case series presented 7 patients with nontraumatic intracranial hemorrhages (ICH) who received dose ranges of 15 to 90 μg/kg. The INR decreased from a mean of 2.7 (range 1.6-5.6) to a mean of 1.1. All patients also received either or both FFP and vitamin K.[18] Two additional patients with subdural hematomas were described in an abstract.[1] A third case series presented perioperative treatment for warfarin-associated CNS hemorrhages in 4 patients (2 with spinal cord hemorrhage, 2 with ICH). Initial INRs ranged from 1.9 to 5.6, and within 2 hours after the administration of rFVIIa (16-22 μg/kg), all INRs normalized. All patients also received FFP. [19] Another case report described a patient with an acute subdural hematoma (rFVIIa dose 120 μg/kg).[20] A patient with cerebral hematoma was reported in a case series (INR of 9.83, decreased to 1.02 with rFVIIa infusion of 4-5 μg/kg/hour × 8 hours). [3] The use of rFVIIa (dose 36-152 μg/kg) was also described in a retrospective case-control series of 81 coagulopathic trauma patients, 9 of whom were on warfarin. The 9 patients sustained traumatic injuries (8 brain and 1 mesentery) and had a survival rate of 44% (4/9) after the administration of rFVIIa. Details involving the extent of decrease in INR and bleeding were lacking in this series. In addition, the patients who received rFVIIa had a higher mortality than coagulopathic controls.[21] A retrospective chart review of 15 patients with warfarin-associated ICH showed that the 12 patients who received rFVIIa in addi-

tion to FFP and Vitamin K had a faster correction of their INR when compared to patients who received FFP and vitamin K alone (8.8 hours in rFVIIa, FFP and vitamin K group versus 32.2 hours in FFP and vitamin K group).[22] The 5 remaining reports looking at the use of rFVIIa in warfarin-associated coagulopathy were not related to CNS bleeds. In a prospective observational study, 16 non-hemophiliac patients on warfarin with acute major bleeding events received rFVIIa (dose range 11-25 μg/kg). A rapid decrease in the INR and a decrease in bleeding was observed in 14 of the 16 patients. All patients also received FFP, and 13 of the 16 received vitamin K.[23] A prospective case series of 13 patients with elevated INR values and bleeding who were treated with rFVIIa (15-90 μg/kg) found an immediate reduction in the INR (0.73-7.37) and cessation of bleeding.[24] A retrospective database (hemostasis.com) review of patients receiving rFVIIa to manage bleeds related to the use of anticoagulant therapy reported 1 successfully treated warfarin-related case. [25] Another case report described correction of the INR in an elderly patient with rVIIA followed by rt-PA administration for a stroke.[26]

Based on this review, we conclude that rVIIa appears to rapidly correct the INR; however, its clinical impact on bleeding in patients taking warfarin remains unclear. This conclusion is based on the observation that currently available evidence consists mainly of small (1-16 patients), non-randomized, retrospective, case series and case reports without adequate controls. Furthermore, the majority of the studies include the use of standard modalities (FFP and vitamin K), which will also impact bleeding. We thus recommend against routine use of rFVIIa in acute warfarin reversal (Grade 2C).

Disclosures

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