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Clinical Reviews

THE CLINICAL USE OF PROTHROMBIN COMPLEX CONCENTRATE

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□ **Abstract—Background: Prothrombin complex concentrate (PCC) is an inactivated concentrate of factors II, IX, and X, with variable amounts of factor VII. Guidelines recommend the use of PCC in the setting of life-threatening bleeds, but little is known on the most effective dosing strategies and how the presenting international normalized ratio affects response to therapy. Objectives: This review aims to highlight available data on monitoring techniques, address shortcomings of currently available data, the reversal of life-threatening and critical bleeds with PCC, and how this product compares to other therapeutic options used in critically ill patients. Discussion: PCC has been identified as a potential therapy for critically bleeding patients, but patient-specific factors, product availability, and current data should weigh the decision to use it. Most data exist regarding patients experiencing vitamin K antagonist-induced bleeding, more specifically, those with intracranial hemorrhage. PCC has also been studied in trauma-induced hemorrhage; however, it remains controversial, as its potential benefits have the abilities to become flaws in this setting. Conclusion: Health care professionals must remain aware of the differences in products and interpret how three- versus four-factor products may affect patients, and interpret literature accordingly. The clinician must be cognizant of how to progress when treating a bleeding patient, propose a supported dosing scheme, and address the need for appropriate factor VII supplementation. At this point, PCC cannot be recommended for first-line therapy in patients with traumatic hemorrhage, and should be reserved for refractory bleeding until more data are available.** © **2013 Elsevier Inc.**

□ **Keywords—prothrombin complex concentrate; factor IX concentrate; warfarin; trauma; thromboelastography**

INTRODUCTION

Vitamin K antagonist (VKA) utilization has steadily risen in the past 20 years, increasing by 300% from 1993 to 2008 alone. VKAs are used for stroke risk reduction in patients with atrial fibrillation and mechanical heart valves, prevention of recurrent embolism after venous thromboembolism, and for treatment of genetic coagulation disorders (1). Trials in a variety of clinical settings have demonstrated a significant risk of bleeding with warfarin, which was as high as 1–3% per year of fatal or life-threatening bleeding in high-risk patients (2). International normalized ratios (INR) > 4 are associated with an increased absolute risk of intracranial hemorrhage (ICH), which can be as much as 2% per year. Continuation of elevated INR values for the initial 20 h post-ICH lead to increased risk of hematoma expansion, an independent risk factor of mortality (3).

Despite the introduction of newer oral anticoagulants, VKAs are still projected to play an important role in anticoagulation; therefore, it is imperative to maintain therapeutic options for bleeding reversal (4). Historically, the preferred method for VKA reversal has been vitamin K supplementation combined with blood products or recombinant factors. Interest has shifted to the potential benefit of using clotting factor concentrate for rapid, reliable, and sustained reversal of life-threatening hemorrhage in these patients.

Guidelines recommend prothrombin complex concentrate (PCC) use for life-threatening bleeds, but little is known concerning the most effective dosing strategies

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or the effect of presenting INR on response to therapy (5). PCC is an inactivated concentrate of factors II, IX, and X, with variable amounts of factor VII. The aim of this review is to highlight available data concerning PCC, including monitoring techniques, reversal of life-threatening bleeds, and comparison with other therapeutic options. Shortcomings of currently available data will also be addressed.

DISCUSSION

Warfarin and Reversal Therapies

Warfarin inhibits vitamin K epoxide reductase enzyme, thus preventing reactivation of the vitamin K-dependent clotting factors II, VII, IX, and X, and the endogenous anticoagulant proteins C and S. Reversal of this mechanism is accomplished through administration of vitamin K or exogenous clotting factor supplementation. Vitamin K, administered intravenously or orally, is the treatment of choice for patients presenting with an elevated INR without signs of clinical bleeding. Patients presenting with clinically relevant bleeding and an elevated INR should receive intravenous vitamin K and an exogenous clotting factor formulation. The most common products utilized for the reversal of VKAs include fresh frozen plasma (FFP), activated recombinant factor VII (rFVIIa), and PCC (6).

FFP

FFP is a plasma-derived blood product containing all clotting factors, as well as approximately 400 mg of fibrinogen. For years, FFP has been the standard of care for reversal of VKA-induced coagulopathy in critically bleeding patients. FFP's shortcomings include the volume associated with its use, risk of transfusion reactions, and time to treatment due to thawing requirements. Each unit of FFP consists of approximately 250 mL and requires an hour to thaw, which can significantly delay therapy in patients presenting with significantly elevated INRs. Patients may receive up to 2 L of volume, as they often require multiple units (7).

rFVIIa

rFVIIa is recombinant human factor VII that enables homeostasis through activation of the extrinsic pathway, resulting in promotion of fibrin formation and decreasing INR (8). rFVIIa is used off label for VKA reversal, trauma-induced coagulopathy, surgery-induced coagulopathy, cardiothoracic surgery, and ICH. Dosing recommendations are variable, with package insert recommendations ranging from 35 to 70 μg/kg and literature from clinical trials ranging from 20 to 90 μg/kg. rFVIIa has been correlated with a significantly increased risk of arterial thrombosis, including myocardial and cerebral infarctions, due to its potent thrombogenecity (9,10).

PCC

Unlike serum-containing products such as FFP, PCC products are lyophilized. This allows PCC to be reconstituted, as opposed to thawing, providing a significant advantage in time to administration. Virtually all products contain factors II, IX, and X, with variable amounts of factor VII. Variation in factor VII concentrations in PCC has led to their classification as either three- or four-factor. PCC concentration of vitamin K-dependent clotting factors is approximately 25 times higher than plasma. In terms of clotting factor concentration, 2000 mL of FFP is comparable to a dose of PCC. To combat the risk of thrombosis postulated with this rapid and concentrated infusion of procoagulant factors, some PCCs contain anticoagulants such as protein C, protein S, and heparin (Table 1) (6).

PCC has been used for years in the treatment of hemophilia, but its use has recently expanded to VKA reversal in patients either actively bleeding or at a high risk of bleeding (11,12). PCC use in acute hemorrhage has been hypothesized to be a more effective, beneficial, and cost-effective alternative to currently available therapy. These advantages may result from a more potent, sustainable, and rapid INR reversal when compared to agents such as FFP. Along with heightened interest in the use of PCC comes a plethora of questions on how to use these agents appropriately, especially in the United States (US).

Monitoring Techniques

When determining a patient's coagulation status, prothrombin time (PT), INR, and partial thromboplastin time (PTT) are evaluated. PT and INR utilize the extrinsic pathway to determine time required to clot, and PTT measures how quickly the intrinsic pathway is activated.

The use of INR has become an important monitoring parameter in the anticoagulated and bleeding patient, despite lack of validation outside the monitoring of VKA patients. INR has been shown to correlate well with the level of inhibition of clotting factor formation. However, its correlation with reversal of clotting factor deficiency is much weaker (3,13,14).

When a patient is initiated on VKA therapy, INR is utilized under the assumption that after reaching a therapeutic level, there is a similar reduction in factors II, VII, IX, and X. Along with this reduction in factors, it is assumed that the intrinsic pathway is being inhibited to a similar