RECOMMENDATIONS FOR USE OF PROTHROMBIN COMPLEX CONCENTRATES IN CANADA

Final. May 16, 2014

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Background:
The National Advisory Committee on Blood and Blood Products (NAC) is an interprovincial medical and technical advisory body to the provincial and territorial health ministries and the blood supplier Canadian Blood Services (CBS). Its mandate is to provide professional leadership in assisting in identifying, designing and implementing cost-effective blood utilization management initiatives for the optimization of patient care throughout Canada. In 2008, NAC was approached by CBS and the Provinces to develop national recommendations for appropriate use and distribution of the first prothrombin complex concentrate (PCC) available in Canada, octaplex®. Since that first recommendation document, two national audits of octaplex® and licensure of a second product, Beriplex® P/N has occurred. These events resulted in the 2011 revision of the Prothrombin Complex Concentrate. Due to a commitment of the National Advisory Committee to review this recommendation framework on a regular basis or when new data becomes available, the working group reconvened in January of 2013. Key areas of evaluation on this review were: dosing recommendations, use of PCC in elective situations and improving the clarity around various recommendations.

Both octaplex® and Beriplex® P/N can be classified as four factor prothrombin complex concentrates. They are both human plasma derived products that have undergone solvent/detergent treatment and/or nanofiltration for viral, bacterial and parasite inactivation and removal. They contain not only the procoagulant Vitamin K dependent factors – II, VII, IX and X – but also contain the anticoagulant factors Protein C, Protein S and Heparin to varying degrees. In addition, Beriplex® P/N also contains Antithrombin. This group is not recommending one product over the other but we recommend not mixing the two products within the same infusion. There is, however, no evidence to suggest that infusing a second dose of the alternate product would be detrimental.

Both of the manufacturers recommend their product when rapid correction of prothrombin complex levels is necessary, such as major bleeding or emergency surgery. For management of vitamin K antagonist treatment with an elevated INR but without bleeding, clinicians are referred to the ACCP 2008 recommendations. In most of these cases, reduction of the dose of the vitamin K antagonist and/or administration of Vitamin K_1 is usually sufficient for patient management.

The working group continues to advocate the use of this product under the supervision of physicians who have access to expertise in thrombosis/hemostasis/transfusion medicine and to adequate diagnostic and treatment facilities to ensure appropriateness of indication, dosing of the product and management of its potential complications. It is critical to recognize that the use of prothrombin complex concentrates may unmask thrombotic risk factors that were being managed through the use of Vitamin K antagonists. These recommendations consider available literature, audit data and consensus opinion of the working group. The lack of strong randomized control trial evidence on clinical effectiveness, morbidity and mortality highlights the need for ongoing data collection on outcome data to ensure best practice. Conflict of interest disclosures of the working group members are available on the NAC website (www.nacblood.ca).

Indications:

Recommended in:

A. Rapid reversal of warfarin therapy or vitamin K deficiency in patients exhibiting major bleeding manifestations.

B. Rapid reversal of warfarin therapy or vitamin K deficiency in patients requiring urgent (< 6 hours) surgical procedures.

Please note: The 6 hour time frame in this recommendation reflects the half life of the product and is not a statement regarding the urgency of the surgery.

Contraindicated in:

A. Patients with a history of heparin induced thrombocytopenia

Not generally recommended* for:

A. Elective reversal of oral anticoagulant therapy pre – invasive procedure.

B. Treatment of elevated INRs without bleeding or need for surgical intervention.

- For management of vitamin K antagonist overdose with elevated INR but without bleeding, please refer to the ACCP 2008 recommendations.

C. Massive transfusion

D. Coagulopathy associated with liver dysfunction

E. **Patients with recent history of thrombosis, myocardial infarction or disseminated intravascular coagulation (DIC)**

Special patient populations*:

A. Pregnant women – there is insufficient published evidence available to allow a recommendation for use or dosing of these products in this patient population. Caution should be exercised if used in pregnancy, particularly in the peripartum / early postpartum period because of heightened tendency to thrombosis**.**

B. Pediatric patients – although anecdotal reports of use in pediatric patients are present, there is insufficient published evidence available to allow a recommendation for dosing and/or use of these products in this patient population**.**

C. Congenital factor II or X deficient patients – use and dosing of these products should be at the discretion of the local Hemophilia clinic**.**

D. **Reversal of direct thrombin inhibitors (DTI) –** there is insufficient published evidence available to allow a recommendation for use or dosing of these products for the reversal of DTI (ie. dabigatran) therapy.

E. Reversal of Direct anti-Xa – there is published evidence suggesting that PCCs may be effective in the reversal of direct anti-Xa (ie. rivaroxaban) therapy in animal studies and in healthy volunteers but no consensus on dosing has been achieved.

** There may be extenuating clinical circumstances necessitating use of prothrombin complex concentrates in these clinical situations. They should be evaluated on a case-by-case basis with a physician experienced in the use of this product. If the decision is to use the product off-label in liver dysfunction and DIC, please consult the product monograph for further recommendations (e.g. the need for antithrombin levels or replacement).*

Dosing, Administration & Monitoring:

There is significant variability in the dosing used for these products across Canada and in the literature.

- The working group felt that there was insufficient published evidence to indicate one dosing regimen as superior to another and recommends following local policy with monitoring for efficacy.
- Some of the variability in practice and literature stems from different target INRs for various clinical indications and whether or not weight based dosing was deemed important by local clinical groups.
- Previous consultation with the Canadian Neurosciences Federation resulted in a recommendation for a target INR of 1.5 for cases demonstrating warfarin associated intracranial hemorrhage but this target can range from 1.2 - 1.7 in other published guidelines.
- It is important to note that the package insert recommendations aim to correct factor levels to normal despite the fact that normal hemostasis does not require 100% factor levels.

SAMPLE dosing schedules for adult patients (if local policy is not already established and deemed appropriate):

1. Standardized single dose**:** The 2008 NAC recommendation utilized a standardized dose of 1000 IU (40 mL) regardless of weight or INR with two goals – minimize thrombotic complications and ensure adequate national inventory.
   - The working group would like to highlight that 50% of patients in the 2010 national audit responded to the previously recommended standardized dose of 1000 IU (40 mL) regardless of weight or INR.
   - Standardized single doses of 25 IU/kg or 40 IU/kg have also been reported in the literature.

2. INR based dosing**:** The 2011 NAC recommendation based the dosing of prothrombin complex concentrate on the INR as per the table below but stated that if the INR is unknown and major bleeding is present, 2000 IU (80 mL) should be administered.

	PCC dose if INR > 5	**PCC dose if INR 3-5**	**PCC dose if INR <3**
Dose	3000 IU (120 mL)	2000 IU (80 mL)	1000 IU (40 mL)

3. ** Dose Banding using both weight and INR (for approx. INR target 1.5)**:**

Weight (kg)	**PCC dose if INR > 6 (40 units/kg)**	**PCC dose if INR 3-6 (30 units/kg)**	**PCC dose if INR 2-2.9 (20 units/kg)**
35-37	1500 IU (60 mL)	1000 IU (40 mL)	500 IU (20 mL)
38-41	1500 IU (60 mL)	1000 IU (40 mL)	1000 IU (40 mL)
42-43	1500 IU (60 mL)	1500 IU (60 mL)	1000 IU (40 mL)
44-56	2000 IU (80 mL)	1500 IU (60 mL)	1000 IU (40 mL)
57-58	2500 IU (100 mL)	1500 IU (60 mL)	1000 IU (40 mL)
59-62	2500 IU (100 mL)	2000 IU (80 mL)	1000 IU (40 mL)
63-68	2500 IU (100 mL)	2000 IU (80 mL)	1500 IU (60 mL)
69-75	3000 IU (120 mL)	2000 IU (80 mL)	1500 IU (60 mL)
76-87	3000 IU (120 mL)	2500 IU (100 mL)	1500 IU (60 mL)
88-91	3000 IU (120 mL)	2500 IU (100 mL)	2000 IU (80 mL)
92-112	3000 IU (120 mL)	3000 IU (120 mL)	2000 IU (80 mL)
113-136	3000 IU (120 mL)	3000 IU (120 mL)	2500 IU (100 mL)
137 or greater	3000 IU (120 mL)	3000 IU (120 mL)	3000 IU (120 mL)

**Doses are rounded up or down to nearest multiple of 500 units (20 mL vial). Single doses should not exceed 3000 units.

Administration: Must be administered intravenously.
May be administered by direct IV push, syringe pump, or minibag.
The manufacturers'recommended maximal rates of infusion are:

- octaplex® = 3mL/min
- Beriplex® P/N = 8 mL/min.

The treating clinician / clinical team must ensure the timely administration of PCC in patients with major bleeding manifestations.

- Individual institutions should adopt a process to facilitate the rapid availability and delivery of PCC for patients with major bleeding manifestations. This may include expedited approval processes for subgroups of patients; pneumatic tube delivery of product or a limited supply of PCC in Emergency departments (if appropriate storage and record keeping to ensure traceability as required by CSA standards can be met in the latter situation).

Vitamin K: Vitamin K_1 (10 mg IV) co-administration is strongly recommended if reversal is required for longer than 6 hours (the half life of PCC). The onset of action of Vitamin K_1 is 4-6 h IV.

- The working group recognizes that institutional policy may preclude the use of intravenous Vitamin K_1 administration. When oral Vitamin K_1 is used as an alternate, the injectable formulation, which can be given orally or intravenously, is preferred. Intramuscular and subcutaneous routes of Vitamin K_1 administration are not recommended.

Post dose monitoring: 1. **INR values** - Since dose effect is not universally applicable, efficacy of dosing must be determined using the surrogate marker of an **INR – 10-30 minutes post PCC administration**.

- If correction to an INR <1.5 has not been achieved and there is insufficient time to wait for Vitamin K to take effect, a subsequent dose of PCC may be required if the patient continues to demonstrate clinical bleeding.

2. **Clinical outcomes** - including evaluation of mortality and thrombotic events, at 24 hours and 30 days post dose.

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