Prothrombin Complex Concentrate

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Rationale for use

Supratherapeutic INR and major bleeding secondary to warfarin therapy occurs in up to 6.5% of anticoagulated patients per year[1]. Fatalities secondary to intracranial hemorrhage occur in approximately 1% of anticoagulated patients annually.[1-5] Warfarin is a vitamin-K dependent clotting factor inhibitor, specifically Factors II, VII, IX, and X. The goal of urgent warfarin reversal, therefore, is to increase the available amount of Vitamin–K dependent clotting factors which will lead to a decrease in INR.

Current treatment options for reversal of supratherapeutic INR include withholding warfarin, administering oral or intravenous vitamin K, fresh frozen plasma (FFP), and prothrombin complex concentrate (PCC). (See Table I)

FFP allows for the exogenous replacement of factors II, VII, IX, and X.[6] Although few studies have been conducted to determine optimal dosing, the convention is to administer FFP at a dose of 15 mL/kg[7], but in the setting of volume overload, this dose may be difficult to administer. The rate of administration of FFP should not exceed 600 mL/hour meaning in a patient weighing 100 kg, at a dose of 15 mL/kg, it would take 2.5 hours to infuse the entire dose. In a patient with a supratherapeutic INR and an intra-cerebral hemorrhage a rapid reduction in the INR would be indicated and the use of FFP in this setting would therefore not be an optimal approach. Additionally, treatment delays may occur as FFP must be thawed prior to use and, since it contains isohemagglutinins, it must be blood group specific.

The use of PCC is now recommended for severe bleeds by several organizations and their respective consensus guidelines, including the American College of Chest Physicians. (see Table IV) PCCs are intermediate-purity pooled plasma products that were previously used for the management of hemophilia B prior to the availability of recombinant factor IX concentrates.[8] All of the currently available PCC products contain factors II, IX, and X with variable amounts of factor VII, protein C, and protein S (see Table II).

Per Chest guidelines, PCC is recommended in patients anticoagulated with vitamin K antagonists (warfarin) who present with a serious or life-threatening bleed at any INR. When used at appropriate doses (25–50 units/kg), INR should begin to decline within 10 minutes of PCC injection and the duration of effect is equivalent to the duration of endogenous clotting factors (see Table III).[9]

Advantages of PCC vs. FFP:[10]

More effective and rapid correction of INR
Greater increase in clotting factors
Can be infused faster than FFP and with less volume
Fewer complications secondary to fluid overload

Shorter preparation time since PCC does not need to be thawed as FFP does
Does not require blood-type matching

Dosing of PCC

Although questions persist regarding the minimum effective dose and the maximum safe dose, the average dose recommended for reversal of supratherapeutic INR is 25–50 units/kg, based upon the factor IX component. Each of the PCC formulations contain varying amounts of factors II, VII, IX, and X. (see Table II) Additionally, the amount of factor varies between vials of the same preparation.

Summary

The use of Prothrombin Complex Concentrates (PCC) should be considered in patients who present with a supratherapeutic INR and serious bleeding and who require rapid reversal of INR. At a dose of 25–50 units/kg, significant INR reduction will likely be seen within 10 minutes of administration.

Reduction in INR with vitamin K (IV or PO) will not be evident until approximately 18–24 hours after vitamin K administration, and large doses of vitamin K may lead to a hypercoaguable state which could last for a week or more, thereby increasing the risk of thrombosis in susceptible patients.

Fresh frozen plasma (FFP) may take hours to infuse, may complicate patient care by increasing volume overload, may lead to treatment delay since FFP must be thawed prior to administration and, since it contains isohemagglutinins, it must be blood group specific.

Recombinant factor VIIa, although not discussed here, may also be used. However, rFVIIa has a short duration of action (approx. 4 hours), and therefore may need to be re-dosed multiple times to maintain the reduction in INR.

Table 1 - Chest guidelines for management of supratherapeutic INR[11]

Management of Supratherapeutic INR or Bleed due to Warfarin Therapy	
Condition	**Description**
INR > therapeutic < 5 No significant bleed	Lower or hold warfarin dose, increase frequency of monitoring, resume warfarin at lower dose once therapeutic
INR ≥ 5 but ≤ 9; No significant bleed	Omit next 1–2 doses, monitor more frequently, resume at lower dose once therapeutic. May administer Vitamin K PO at a dose of ≤ 5mg if at increased risk of bleed. Will take approximately 24h to see reduction in INR after PO Vitamin K
INR ≥ 9 No significant bleed	Hold Warfarin and give 5–10 mg Vitamin K PO x 1. INR should be substantially reduced within 24–48 hours.
Serious bleed @ any INR	Hold Warfarin. Administer 10mg Vitamin K IV x 1 via slow infusion. Supplement with FFP or PCC, depending up on urgency of situation. Recombinant Factor VIIa may be considered. May repeat IV vitamin K q12h if necessary
Life threatening bleed	Hold warfarin. Give PCC supplemented with 10mg IV Vitamin K via slow infusion. Recombinant Factor VIIa may be considered as alternative to PCC. Repeat if necessary, depending on INR.

Table II - Available preparations and dosing of PCC[9]

	FII	FVII	FIX§	FX	Dose*¶
3-Factor PCC					
Prothrombinex HT (Australia)	100 units	-	100 units	100 units	25–50 units/kg
Bebulin (USA)	120 units	13 units	100 units	139 units	25–35 units/kg (minor bleed) 40–55 units/kg (moderate bleed) 60–70 units/kg (serious bleed)
Profilnine SD (USA)	148 units	11 units	100 units	64 units	25–50 units/kg
Cofact (Europe and UK)	~75 units	~25 units	100 units	~75 units	25–50 units/kg
4-Factor PCCs					
Beriplex (UK)	128 units	68 units	100 units	152 units	25–50 units/kg
Prothromplex T (Austria)	100 units	85 units	100 units	100 units	25–50 units/kg
Octaplex (UK and Europe)	44–152 units	36–96 units	100 units	72–120 units	25–50 units/kg
PPSB-HT (Japan)	100 units	100 units	100 units	100 units	25–50 units/kg

§Units of factors are ratio-based as compared to factor IX, e.g., Bebulin contains 120 units of factor II for every 100 units of factor IX.
*Dose of PCC product is based upon factor IX component
¶Rate of administration should not exceed 2 mL/minute

Table III - Half-life of vitamin K dependent clotting factors

	Factor II	Factor VII	Factor IX	Factor X
T 1/2 elimination (h)	60	4.2	17	31

Duration of action of exogenously administered factors equal to that of endogenously produced factors.

Table IV

Current Recommendations for the use of PCCs for warfarin reversal
US 7th ACCP Consensus Conference on Antithrombotic Therapy[11] •PCCs or rFVIIa for serious or life-threatening bleeding at any INR
UK Guidelines on Oral Anticoagulation[12] •PCCs (50 units/kg) for major bleeding
Australian Consensus Guidelines on Warfarin Reversal[13] •PCCs for clinically significant bleeding, or •PCCs for INR > 9 without bleeding
Italian Federation of Anticoagulation Clinics[14] •PCCs for serious bleeding (e.g., CNS, gastrointestinal)

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