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Letter to the Editors-in-Chief

Prothrombin complex concentrate (PCC, Octaplex®) in patients requiring immediate reversal of vitamin K antagonist anticoagulation

Dear Editors,

Warfarin is the vitamin K antagonist (VKA) used in oral anticoagulant therapy (OAT) for prevention and treatment of thrombosis and is monitored by the international normalized ratio (INR). When immediate reversal of anticoagulation is necessary, vitamin K and fresh frozen plasma (FFP) are administered [1]. Some prothrombin complex concentrates (PCCs) may be more effective than FFP and vitamin K for correction of INR in warfarin-treated patients with life-threatening bleeding [2,3]. A PCC available in Canada is Octaplex®, freeze-dried, solvent/detergent (S/D) treated and nanofiltered to remove pathogens which contains coagulation factors II, VII, IX, and X and proteins C and S at concentrations of 14–38 IU/mL, 9–24 IU/mL, 25 IU/mL, 18–30 IU/mL, 7–31 IU/mL, and 7–32 IU/mL, respectively . According to the National Advisory Committee on Blood and Blood Products, use of this PCC is limited to facilities adequately equipped to evaluate patient symptoms as requiring reversal of anticoagulation [4].

Methods

Study design and plan

This study was a retrospective chart review held at St. Joseph's Hospital in Hamilton, Ontario, Canada.

Study objectives

The primary goal of the review was to determine the efficacy of Octaplex® in reversing VKA anticoagulation, specifically warfarin. This was done by using previous laboratory results from patient charts such as INR and activated partial thromboplastin time (aPPT) values. Reduction in INR was the primary endpoint of this evaluation.

Patients

This project was approved by the hospital Research Ethics Board at St Joseph's Healthcare, Hamilton. Consent was waived as this was a quality assurance project. A list of all patients who had received Octaplex® was obtained from the Transfusion Medicine service. As this service is the sole provider of this project this list was comprehensive and inclusive. Data was requested from the start of use of Octaplex® (November 2008) until the start of this project (May 2010). Patient charts from that time period were reviewed and all patients who had received Octaplex® and were also currently taking warfarin were included in the review. Although these guidelines did not allow for screening based on indication of hospitalization, all patients who met these criteria had indications that closely resembled the inclusion criteria that are used in prospective studies regarding PCC efficacy: a bleed, needing rapid INR reversal prior to surgery or an excessively elevated INR.

Laboratory methods

Laboratory parameters from patient charts were abstracted including the INR, aPPT and complete blood count (CBC). These tests were ordered by physicians in the course of their usual patient care and as such the pattern of tests is dissimilar amongst the patients. Only one patient of the sample of 85 events had assays completed for blood factors II, V, VII, and X both before and after Octaplex® infusion.

Results

Patients

Eighty-two patients (33 females) treated by Octaplex® and on warfarin between November 2008 and May 2010 with a mean age of 71.9 (42–93) years were reviewed. Indications for anticoagulation included atrial fibrillation (n = 57) venous thromboembolism (n = 33), mechanical heart valve (n = 12), myocardial infarction (n = 4), dilated cardiomyopathy, HIV-associated hypercoagulable state, mesenteric ischemia, iliac thrombus, recurrent clotting of an AV fistula and unknown (1) (Table 2). A total of 85 doses were administered. Table 1 presents data in patients with bleeding (36/85), needing urgent surgery (40/85) or with an excessively elevated INR (8/85) as well as the mean dose of Octaplex® for each group. One patient received Octaplex® for an unknown indication. Another patient who presented with bleeding received an unknown final dose of Octaplex® and was thus omitted from analysis. Six patients did not have coagulation testing performed after PCC administration and were omitted. None of the excluded patients died or sustained a thromboembolic event.

Octaplex® Administration

Octaplex® doses ranged from 1000 to 3500 IU with a mean dose of 1792 ± 601 IU. Dosage was variable as it was individualized according to patient body weight and INR. Patients presenting with excessively elevated INR values received higher average doses of Octaplex® (2188 ± 556) than patients receiving Octaplex® for bleeding (1914 ± 692) or surgery (1612 ± 494). An average dose of 4.9 ± 5.49 mg of vitamin k (range 1 – 50 mg) was given to 69/85 patients within a mean of 22:06 hours of Octaplex® (range

Abbreviations: VKA, Vitamin K antagonist; FFP, Fresh frozen plasma; PCC, Prothrombin complex concentrate; INR, International normalized ratio; OAT, Oral anticoagulant therapy; TACO, Transfusion associated cardiac overload syndrome; TRALI, Transfusion related acute lung injury; aPPT, Activated partial thromboplastin time; CBC, Complete blood count; AV, Arteriovenous; CAD, Canadian dollars.

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0:00 – 222:11 hours), administered intravenously where documented.

INR

Patients treated for excessively elevated INR had the highest average baseline INR values (10.4, range 1.2 – 25) whereas INRs in bleeding (5.83, range 1.6 – 25) and surgical patients (3.01, range 1.2 - 10) were lower. Amongst all patients, INR decreased significantly from 5.08 ± 5.39 (range 1.2 – 25) to 1.43 ± 0.42 (range 0.9 – 3.3) ($p<0.0001$), with post-infusion INR measurement taken at an average of 894 minutes after Octaplex® infusion (range 5 – 6685 min.) (Fig. 1). The procoagulant effect of PCCs is immediate – delays in obtaining post-infusion INR measurement were related to clinical issues which supervened over obtaining repeat INR values. Forty-seven of seventy-nine [59.5%, 95% CI 47.9 to 70.4%] administrations resulted in an INR of 1.3 or less and 60/79 [75.9%, 65.0 to 84.9%] resulted in an INR of 1.5 or less. A trend to an increase in the mean INR was observed from day 1 to day 3 post infusion in bleeding patients (1.34 to 1.55, $p=0.27$), and in high INR patients (1.38 to 1.8, $p=0.49$). This was not seen in patients requiring urgent surgery (1.43 to 1.48) ($p=0.46$). An increase in the INR suggests inadequate vitamin K doses at the time of reversal although a comparison of rate of change of INR (percent decrease in INR/minute) showed no significant difference between patients receiving (mean 12.8% decrease INR/min., $n=65$) and those not receiving vitamin K (mean 19.4% decrease INR/min., $n=8$).

The aPPT decreased significantly in all patients from 55.6 ± 30.6 s to 36.6 ± 8.3 s ($p<0.0001$), taken at an average of 489 minutes after Octaplex® infusion (range 5 – 6685 min.). Coagulation factor assays were completed for one patient, a 50 year old female who presented with an INR in excess of 25 (Fig. 2). Factor V levels are preserved despite the elevated INR – levels of the vitamin K dependent factors (II, VII and X) rise rapidly with infusion and correlate with decreasing INR. Coagulation factors then decrease as infused factors are consumed and the warfarin effect (as indicated by rising INR) again becomes manifest. Consistent with its half-life, the level of factor VII falls most rapidly over time (3–4 hr); factors II, IX and X fall slower due to their longer half-lives (60, 18–24 and 40–45 hr respectively) [5].

Platelet counts

Platelet counts were available for 64 infusions. Platelet counts decreased significantly from 233,781 ± 101,000/μL to 209,391 ± 82,431/μL ($p=0.0004$) at a mean of 526 ± 514 minutes after administration of Octaplex®.

Deaths

Seven patients died during hospitalization after receiving Octaplex®. Four were given Octaplex® prior to surgery. One was an 87 year old male with end– stage liver disease and sepsis; surgery was deferred for palliative care. The second was an 89 year old female requiring urgent exploratory laparotomy, however, after Octaplex® was administered her family declined the surgery and she was subsequently treated palliatively. The third, an 82 year old male with Fournier's gangrene who underwent debridement, became septic afterwards and care was withdrawn. The fourth, a 70 year old female with metastatic sarcoma who underwent laparotomy, was followed by palliative care and expired due to intra-abdominal sepsis. Three patients who received Octaplex® for bleeding died. The first was an 84 year old male with renal failure and an upper GI bleed. After a complex hospital stay (precipitated by loss of dialysis access) the patient had care withdrawn. The second was a 77 year old female admitted with a hemorrhagic stroke. She received the PCC but died later the same day as a consequence of the intracerebral bleed. The last patient, a 73 year old male with an upper GI bleed following a renal transplant, post-operatively developed urosepsis and care was eventually withdrawn.

Table 2
Average change in INR and vitamin K administration. Average change in INR data are limited by the observation that patients with lower INR values were less likely to receive vitamin K (and thus had lesser prolongations in the INR to correct). The figures in the second part are summative, therefore for the 4 patients who had an INR within the three times noted their total INR fall, on average, was (4.415 + 1.771 + 2.250 or 8.436). The greatest numerical fall in the INR is attributable to the PCC with later falls of lesser magnitude being attributable to vitamin K.

	Vitamin K (64)			Without Vitamin K (9)
Average Change in INR	3.975 ± 5.857			1.767 ± 1.609
Time After Octaplex® Administration	<6 hrs (53)	6-12 hrs (7)	12-24 hrs (4)	
Average Change in INR	4.415 ± 6.342	1.771 ± 1.212	2.250 ± 1.370	

Thromboembolic Events

Three patients experienced later thromboembolic events after administration of Octaplex®. Follow up was not standardized and ascertainment of thromboembolic events was not systematic. The first patient, a 46 year old female, had venous clot extension of a previously diagnosed left leg DVT 8 days after PCC administration. The second patient, a 50 year old male, had a non-occlusive renal vein clot 8 days after administration. The last, a 75 year old female, developed cilioretinal artery occlusion 238 days after receiving PCC. No other adverse events attributable to PCC were identified in this review.

Discussion

In this study, we found Octaplex® to be effective in quickly lowering INR levels towards the normal range as noted in other studies [6], and normalizing INR pre-operatively for urgent surgery. Although this study did not specifically examine Octaplex® dosing we recommend dosing according to patient body weight and pre-treatment INR

Table 1
Indications for Octaplex®.

Indication	Bleeding (36)	Surgery (40)	Elevated INR (8)
	GI bleed (16) Generalized bleed (7) Intracranial bleed (4) Hematoma (9)	Orthopedic (fracture,arthroplasty) (5) Laparotomy, bowel resection (4) Thoracentesis (4) Percutaneous renal surgery (4) Urologic surgery (4) Renal transplant (3) Vascular surgery (3) Other (13)	INR ≥ 25 (2) 24 ≥ INR ≥ 8 (2) INR ≤ 7 (4)
Octaplex® Dose (IU)	1914 ± 692	1612 ± 494	2188 ± 556