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Review

Prothrombin complex concentrates: a brief review

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Summary

Prothrombin complex concentrates are haemostatic blood products containing four vitamin K-dependent clotting factors (II, VII, IX and X). They are a useful, reliable and fast alternative to fresh frozen plasma for the reversal of the effects of oral anticoagulant treatments (vitamin K antagonists). They are sometimes used for factor II or factor X replacement in patients with congenital or acquired deficiencies. They are widely prescribed in Europe. Several retrospective and prospective studies have demonstrated their efficacy in normalizing coagulation and in helping to control life-threatening bleeding. Few side-effects, mainly thromboembolic events, have been reported. The link between these events and prothrombin complex concentrate infusion has, however, often been brought into question. The use of prothrombin complex concentrates in new promising indications such as the management of massive bleeding requires prospective studies providing a high level of evidence in a high-risk setting.

Keywords: PROTHROMBIN COMPLEX CONTENTRATES; VITAMIN K; HAEMORRHAGE; DISSEMINATED INTRAVASCULAR COAGULATION; BLEEDING; THROMBOSIS; FACTOR IX.

Introduction

Prothrombin complex concentrates (PCCs) are highly purified concentrates with haemostatic activity prepared from pooled plasma. They contain four vitamin K-dependent clotting factors (F) (II (prothrombin), VII, IX and X). Their main authorized indication is reversal of the effects of oral anticoagulants (vitamin K antagonists, VKAs). They are sometimes, albeit rarely, used for replacement therapy in patients with congenital or acquired deficiencies in FII or FX [1]. In several European countries, they are also used in the management of massive peri- and postoperative bleeding [2]. Because of their high potency, they are thought to promote thrombosis, although this is not certain in the case of the latest PCCs.

This review will focus on a description of available PCCs, on their indications, dosages, contraindications and side-effects, and on suggested extensions to their current authorized indications. It will not address activated PCCs for the treatment of patients having clotting factor inhibitors.

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Differences in PCC preparations – pharmacokinetics

In 1998, a guideline of the European Pharmacopeia fixed PCC composition [3]. A PCC should have a minimum FIX potency level, FII and FX potencies that are close to FIX potency and that do not exceed this potency by more than 20%, and lower or much lower FVII potency. The overall clotting factor concentration is approximately 25 times higher than in plasma [4]. Some PCCs contain anticoagulant proteins C and S, and antithrombin (at least 1 IU mL^{-1} per preparation). It is, however, uncertain whether these proteins provide a systemic antithrombotic effect and, even if the addition of antithrombin may seem appropriate, its usefulness has never been confirmed. Most PCCs also contain small amounts of standard heparin (0.5 IU heparin per IU factor IX) to prevent

Table 1. Main characteristics of five European prothrombin complex concentrates [4,6,15,28,29].

	Activities (IU mL^{-1}) (mean or range)				
Company	Baxter	CSL Behring	LFB	Octapharma	Sanquin
Brand	Prothromplex-T®	Beriplex®	Kaskadil®	Octaplex®	Cofact®
Plasma source	United States, Austria, Czech Republic, Germany, Sweden, mostly paid apheresis	United States, Austria, Germany, paid/unpaid	France, unpaid	Sweden, Austria, Germany, United States, unpaid	The Netherlands, unpaid
Viral inactivation	Vapour heat, 60°C for 10 h at 190 mbar, then 80°C for 1 h at 375 mbar	Pasteurization at 60°C, 10 h and nanofiltration	TNBP/ polysorbate 80	TNBP/polysorbate 80 and nanofiltration	TNBP/polysorbate 80 and nanofiltration
Factor IX	30	29	25	25	25
Factor II	24–45	31	37	38	14–35
Factor VII	25	16	10	24	7–20
Factor X	30	41	40	30	14–35
Protein C	7–20	35	32*	31	–
Protein S	–	25	19*	32	–
Protein Z	–	36	–	–	–
Antithrombin	<2	0.6	Traces	–	<0.6
Heparin	<0.2	0.5	5	0.2–0.5	–

*Proteins C and S are not mentioned in the summary of product characteristics of this prothrombin complex concentrate. However, since these activities have been measured by the manufacturer, they should be mentioned.

activation of clotting factors (Table 1). All PCCs undergo at least one step of viral reduction or elimination (solvent detergent treatment, nanofiltration, etc.).

Data on PCC pharmacokinetics are scant. The half-lives of the four clotting factors differ widely. The half-life of FII is much longer (60–72 h) than that of the other factors (6–24 h). FVII has the shortest half-life (approximately 6 h) [5]. The long half-life of FII (prothrombin) needs to be taken into account when considering the potential accumulation of prothrombin after multiple dosing. A recent study of 15 healthy volunteers receiving a single rapid 50 IU kg^{-1} infusion of Beriplex®, a commercially available PCC, showed that, on first sampling at 5 min post-infusion, plasma clotting factor concentrations had increased by a median of 122% (FII), 62% (FVII), 73% (FIX) and 158% (FX) [6]. Proteins C and S also increased rapidly. The median terminal half-life was 59.7 h (FII), 4.2 h (FVII), 16.7 h (FIX) and 30.7 h (FX). The median *in vivo* recovery was 1.57% IU^{-1} kg^{-1} for FIX and >2% IU^{-1} kg^{-1} for the three other clotting factors.

Indications

The main indication of PCCs is treatment of vitamin K-dependent factor deficiency in patients taking VKAs. PCCs are also used to replace FII or FX in patients with congenital or acquired deficiencies.

PCCs in patients taking VKAs

VKAs prevent the regeneration of vitamin K, which acts as a cofactor in the γ-carboxylation of factors II, VII, IX and X, and of anticoagulant inhibitor proteins C, S and Z synthesized in the liver [5]. The anticoagulant effect of VKAs may be reversed by a variety of methods: simple dose omission, vitamin K administration, replacement of the deficient factors using PCC or fresh frozen plasma (FFP) or, as suggested recently, by by-passing the coagulation cascade with recombinant activated factor VII (FVIIa) [4]. The rule is that, whatever the setting, replacement coagulation factors should be given whenever active bleeding occurs. However, PCCs should be used only to prevent or stop bleeding.

Several small studies, especially in patients with intracranial haemorrhage (ICH), have shown that PCCs are better than FFP in reducing the Internationalized Normalized Ratio (INR) response, and that they reverse anticoagulation more rapidly than FFP:

(i) A retrospective study of 17 patients with anticoagulant-related ICH treated by either PCC ($n = 10$) or FFP ($n = 7$) showed that in PCC-treated patients the mean INR fell from 2.83 to 1.22 in 4.8 h, whereas it took 7.3 h for the INR to fall from 2.97 to 1.74 using FFP (i.e. 4–5 times longer) ($P < 0.001$) [7]. Symptoms and signs of ICH, measured on an eight-grade Reaction Level Scale, progressed on average 0.2 grades in patients given PCC compared with 1.9 grades in those given FFP ($P < 0.05$).

(ii) A study comparing PCC and standard treatment (FFP plus vitamin K supplementation) in six patients with ICH has confirmed these observations [8]. The mean INR fell from 4.86 to 1.32

after PCC treatment and from 5.32 to 2.30 after standard treatment [8]. Complete reversal of oral anticoagulation (i.e. complete INR correction) and time to bring about this reversal were significantly better on PCC treatment than standard treatment ($P < 0.001$).

(iii) In a study of orally anticoagulated subjects requiring rapid correction of their haemostatic defect, the INR was completely corrected in 28 out of 29 PCC-treated patients (range 0.9–3.8, mean 1.3), whereas it was incompletely corrected in the 12 FFP-treated patients (range 1.6–3.8, mean 2.3) indicating an ongoing anticoagulated state [9].

However, to date, there is no large prospective, randomized, double-blind, head-to-head comparison of PCC and FPP demonstrating a definitive clinical benefit of PCC over FPP. The debate is ongoing, although many strong arguments currently support PCC use [10]:

- FFP administration (at least 15 mL kg^{-1}) may represent a dangerous overload in fragile cardiac patients or in the elderly. Furthermore, such a plasma volume cannot be infused quickly.
- In a patient who is bleeding, the infusion of a large volume of FFP could dilute platelets and red blood cells, and thus impair primary haemostasis.
- FFP administration requires knowledge of a patient's blood group as it is blood group specific.
- Thawing FFP takes time whereas PCC is immediately available.
- A retrospective study has found that supplementing FFP with PCC does not provide any extra benefit with regard to INR correction [11].

Current guidelines are also in favour of PCC. The British Committee for Standards in Haematology has recently recommended PCC rather than FFP for anticoagulation reversal in patients with major bleeding [12]. The American College of Chest Physicians guidelines recommend only PCC for life-threatening bleeding (grade 1C) [5].

Other indications

Until the availability of specific FII and FX concentrates, PCCs have a marketing authorization for congenital or acquired FII and FX deficiencies. In some special situations (e.g. amyloidosis of the spleen with FX chelation), PCCs may help manage bleeding risk and save lives.

Vitamin K deficiency should only be treated with PCC when bleeding is life threatening. Concomitant vitamin K supplementation must be given [1].

FFP should be preferred to PCCs in the treatment of diminished clotting factor synthesis due to liver dysfunction or after a liver transplant as PCCs do not contain FV. However, PCC infusion may be considered when there is a risk of overload or massive bleeding.

PCC infusion during a major haemorrhage requiring massive transfusions has never been compared to infusion of FFP and/or fibrinogen, and is therefore not recommended even though the practice is widespread in several European countries. It should not be forgotten that PCCs contain no FV, FVIII or fibrinogen, which play a key role in haemostasis. PCCs could be considered for compassionate use, as an adjunct to FFP, when FFP cannot control severe bleeding due to FII deficiency. Dosage and infusion duration will depend on bleeding severity and site [2,13]. Large prospective randomized studies of PCCs are needed in this indication.

Dosage

A first administration of 1 IU of PCC per kg body weight generally increases the plasma activity of FVII and FIX by 0.5–1 IU dL^{-1} and of FII and FX by 1–2 IU dL^{-1}. A second administration increases activity by 1–2 and 2–4 IU dL^{-1}, respectively [14].

The optimal PCC dose to reverse oral anticoagulation therapy and stop bleeding is still unknown. A single dose of 500 IU PCC or even less was initially thought to be sufficient to correct the INR but this opinion has been challenged:

(i) An open, prospective, randomized controlled trial has compared the efficacy of a standard PCC dose equivalent to about 500 IU FIX ($n = 47$) and a tailored dose based on a target INR of 2.1 or 1.5, the initial INR and the patient's body weight ($n = 46$) in patients with major bleeding or admitted for emergency surgery [15]. The target INR value was reached within 15 min of administration by a significantly higher percentage of patients receiving a tailored dose than a standard dose (89% vs. 43%; $P < 0.001$).

(ii) Another study has compared the efficacy of four PCC doses in correcting the INR (200 IU ($n = 6$ patients), 500 IU ($n = 30$), 1000 IU ($n = 3$) and 1500 IU ($n = 3$)) [16]. The 200 IU dose reduced INR significantly in all six patients but the INR nevertheless remained above 2.0 in three of these six patients, thus demonstrating the inadequate efficacy of this dose. A 500 IU dose was optimal in patients with an INR below 5.0 but was inadequate in patients with an INR of 5.0 or more.

Since these two studies, many case reports and small case series have confirmed that an initial PCC bolus of 25–30 IU kg^{-1} is a reasonable option [17,18]. This choice is supported by the results of an open non-randomized study of 10 patients with

major bleeding and an elevated INR value (8.9, 14.4, 15.8, 18.0 in 4/10 patients and >20 in 6/10 patients) [19]. The patients received 30 IU kg^{-1} of PCC (Beriplex P/N; Aventis Behring) and 5 mg of intravenous (i.v.) vitamin K. Bleeding complications were malaena, haematuria, haematemesis, haemoptysis, epistaxis, retroperitoneal bleeding and pulmonary haemorrhage. The median INR after treatment was 1.1. All patients had a satisfactory clinical response with immediate cessation of bleeding. No thromboembolic complications occurred.

However, higher PCC dosages have also been recommended: 25 IU kg^{-1} for an INR of 2.0–3.9, 35 IU kg^{-1} for an INR of 4.0–5.9 and 50 IU kg^{-1} for an INR $\geq$ 6.0 [10]. These dosages were recently tested in a prospective study in 43 patients (26 surgical cases, 17 cases of acute bleeding). They were safe and effective. Within 30 min of PCC infusion, the INR had fallen to 1.3 in 93% of patients [20]. The median INR remained between 1.2 and 1.3 over 48 h.

The question whether a single PCC dose of 25–30 IU kg^{-1} or increasing PCC doses should be preferred has not been settled. Different dosage forms are available in Europe. However, regardless of dosage, because the half-life of FVII is only 6 h, patients should always also receive vitamin K. The oral route should be preferred to the i.v. or subcutaneous route because of the induced allergy risk of the i.v. route.

Thromboembolic risk and other side-effects

Thromboembolism

Case reports published in the nineties have warned against a potential increase in thromboembolic risk after PCC administration [21]. The risks include myocardial infarction, disseminated intravascular coagulation (DIC), arterial thrombosis and deep vein thrombosis. A 1998 review of five fatalities occurring after treatment with a particular brand of PCC concluded that there was a causative link between the product and the deaths [21]. All the patients had undergone surgery, had acquired clotting factor deficiencies and underlying diseases predisposing towards thrombosis or DIC. PCC was administered to prevent bleeding. An interaction between PCC and aprotinin may also have played a role in three of these five patients. Even if the incriminated brand of PCC has since been withdrawn from the market, the risk of thromboembolism with the newer PCCs cannot be ruled out.

A few potential risk factors can be established from an analysis of the adverse events that have occurred:

- some of the PCCs that have given rise to thromboembolic events contain a higher level of FII (prothrombin) than other factors. The longer half-life of FII could lead to accumulation after repeat administration [22]. In an *in vitro* thrombin generation assay using plasma from coumarin-treated patients and PCCs with and without known clinical thrombogenicity, prothrombin was identified as the most likely thrombogenic component with the highest impact upon thrombin generation [23]. The *in vitro* thrombogenicity was completely reversed in the presence of anticoagulant (antithrombin plus heparin).
- FVII might be activated into FVIIa and be responsible for thromboembolic events. It has been shown that high FVII activity tends to be associated with high FVIIa activity and that reducing FVII concentration decreases FVIIa potential activity [24]. PCCs with low FVII activity are capable of controlling severe bleeding effectively [7].
- Most reported thromboembolic events concern patients at high risk of thromboembolism (advanced age, renal insufficiency, atrial fibrillation, recent venous thromboembolism) in whom oral anticoagulants have been withdrawn. They received PCC after a bleeding accident. Since oral anticoagulant withdrawal increases thromboembolic risk, it becomes difficult to attribute the accident to the PCC rather than to a hypercoagulable context in an untreated patient [25]. As soon as oral anticoagulants are withdrawn, and when bleeding is under control, thromboembolic risk should, whenever possible, be reduced by the use of unfractionated heparin or low-molecular-weight heparins [5].

In summary, PCCs should contain antithrombin and heparin to neutralize FIXa and FXa, as demonstrated in animal models [26]; FII (mainly) and FX content should be adjusted to prevent overload due to their long half-lives; FVII concentration should be reduced because of the potential generation of FVIIa; the usefulness of adding proteins C and S to PCCs has not been demonstrated [3]; thromboembolic events are rare and several recent case series have shown that high PCC doses (>40 UI kg^{-1}) are safe even in high-risk patients [27].

Viral transmission

Pre-treatment of PCCs has considerably decreased viral risk. Contamination by non-enveloped viruses is, however, still possible, even if many additional controls with polymerase chain reactions focused on these genomes are performed on the plasma pools before fractionation.

Allergic reactions

As observed with foreign proteins and all blood components, PCCs can induce an acute anaphylactic reaction, even if such events are very rare.

Contraindications

Heparin-induced thrombocytopaenia

Since most PCCs contain very small amounts – or traces – of unfractionated heparin, they should, in theory, not be administered to patients with type II heparin-induced thrombocytopaenia (HIT) or to HIT patients who develop thrombotic complications (HITT). In practice, however, HIT patients are now treated with a single bolus of i.v. heparin when a cardiopulmonary by-pass is scheduled more than 6 months after the first HIT episode since the antibody responsible for the HIT syndrome generally disappears by this time. The situation with PCCs, where only small amounts of heparin are present, may be considered to be analogous. Actually, there is no reported case of a HIT related to a PCC product at all. So the heparin discussion concerning HIT could be understood as theoretical.

Disseminated intravascular coagulation

DIC is the single absolute contraindication to PCC use. The only exception might be patients with an immediate threat to life and substantial clotting factor deficiency when FFP administration is not possible. However, this clinical situation is rare and bears a high risk of thromboembolic events.

Conclusion

At the end of the day, PCCs are powerful haemostatic agents in patients taking VKAs who develop bleeding complications, or prior to an invasive procedure. They are antagonists able to reverse the effect of oral anticoagulants and correct the INR response. PCC dosage forms differ but preparation composition does not. The latest PCCs have a much reduced potential of causing thromboembolic events but are not devoid of thrombogenicity. New indications such as the treatment of massive bleeding need to be evaluated in large academic randomized controlled trials.

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