Prothrombin complex concentrates: an update

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Introduction

Although the various coagulation factors are present at physiological concentrations in fresh-frozen plasma (FFP) derived from healthy blood donors, some virally inactivated plasma-derived coagulation factor concentrates have been available for many years. These latter products include single coagulation factor concentrates (such as factor VIII concentrates for the treatment of haemophilia A and factor IX concentrate for the treatment of haemophilia B) or the so-called prothrombin complex concentrates (PCC), which are intermediate purity pooled plasma products containing a mixture of vitamin K-dependent proteins[1,2].

This review will focus on the description of PCC, on their indications and safety. It will not address activated PCC for the treatment of patients with clotting factor inhibitors.

Prothrombin complex concentrates

PCC are produced by ion-exchange chromatography from the cryoprecipitate supernatant of large plasma pools after removal of antithrombin and factor XI[2]. Different processing techniques involving ion exchangers enable the production of either three-factor (i.e., factors II, IX and X) or four-factor (i.e., factors II, VII, IX and X) concentrates with a final overall clotting factor concentration approximately 25 times higher than in normal plasma[3]. To prevent activation of these factors, most PCC contain heparin. PCC may also contain the natural coagulation inhibitors protein C and protein S. The PCC are standardised according to their factor IX content. All PCC 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)[4]. Importantly, the long half-life of FII (prothrombin) needs to be taken into account when considering the potential accumulation of prothrombin after multiple dosing. PCC are lyophilised, requiring reconstitution in a small volume and can be administered rapidly (e.g. over 10 min).

Two PCC are currently available in Italy: Uman Complex D.I. (Kedrion, Castelvecchio Pascoli, Italy) and Prothromplex TIM 3 (Baxter, Vienna, Austria)[5]. Uman Complex D.I. contains clotting factors II, IX and X and undergoes two steps of viral inactivation: first, solvent/detergent treatment and then heat treatment (100°C for 30 min). Prothromplex TIM 3 also contains three clotting factors (II, IX and X) and is virus-inactivated with vapour heat treatment (60 °C for 10 h, then 80 °C for 1 h). Both products contain small amounts of heparin.

A new PCC, previously named Beriplex P/N, is registered in Italy with the trade name Confidex® (CSL Behring, Marburg, Germany). It is a balanced concentrate, containing a defined concentration of the four vitamin K-dependent clotting factors (II, VII, IX and X) and the thrombo-inhibitor proteins C and S. Interestingly, it is the only PCC containing antithrombin in addition to heparin. Confidex® is derived from human plasma screened by five polymerase chain reaction/nucleic acid amplification tests to detect viral DNA and RNA from hepatitis A, B and C viruses, human immunodeficiency virus-1 and parvovirus B19 and two virus inactivation/removal steps, pasteurization and nanofiltration[6-8], are applied during its production. Table I summarises the main characteristics of these three PCC.

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Table I - Main characteristics of the prothrombin complex concentrates available in Italy*

Brand (Company)	Purification	Viral inactivation	Clotting factors (U/mL)				Anticoagulant proteins (U/mL)			
			II	VII	IX	X	PC	PS	AT	Heparin
Uman Complex D.I. (Kedrion)	Ion-exchange chromatography	Solvent/detergent + 100°C for 30 min	25	-	25	20	-	-	NQ	NQ
Prothromplex TIM 3 (Baxter)	Ion-exchange chromatography	Vapour heat 60°C for 10 h, 80°C for 1 h	30	-	30	30	-	-	-	0.5
Confidex (CSL Behring)	Ion-exchange chromatography	Pasteurization 60°C for 10 h + nanofiltration (75 nm-35 nm)	20-48	10-25	20-31	22-60	15-45	13-38	0.6	0.5

Abbreviations: PC, protein C; PS, protein S; AT, antithrombin; NQ, not quantified.
* In Europe, ranges are usually given on the product label, in accordance with the European Pharmacopoeia; single values are generally from older, national registrations.

Clinical indications of prothrombin complex concentrates

PCC were originally developed for the treatment of patients with haemophilia B; however, due to the availability in the last years of plasma-derived high purity factor IX concentrates and, more recently, of a recombinant factor IX product, their indications have progressively shifted from this bleeding disorder towards the replacement therapy of congenital or acquired deficiency of vitamin K-dependent clotting factors[1]. Indeed, PCC are indicated for the treatment or prophylaxis of bleeding in congenital deficiency of any of the vitamin K-dependent coagulation factors when purified specific coagulation factor products are not available (in Italy factor II and/or factor X deficiency)[9]. However, the main indication for PCC is actually the urgent reversal of over-anticoagulation with warfarin. Vitamin K antagonists act through the inhibition of vitamin K-dependent gamma-carboxylation of coagulation factors II, VII, IX and X and also of the endogenous anticoagulation factors proteins C and S, synthesised in the liver[4]. The primary complication of oral anticoagulant therapy with coumarins is bleeding. In large-scale epidemiological studies on patients receiving oral anticoagulant therapy, the annual incidence of major bleeding complications ranged from 1.1% to 1.5%, gastrointestinal and intracranial sites being most frequently involved (30-60% and 17-30%, respectively)[10,11]. The goal of urgent warfarin reversal is to raise the levels of or replace vitamin K-dependent clotting factors[12]. Four options are available for the reversal of oral anticoagulant therapy: withholding the vitamin K antagonist, administration of oral or intravenous vitamin K, replacement of the deficient factors using PCC or FFP and, as recently suggested, by by-passing the coagulation cascade with recombinant activated factor VII (rFVIIa)[13,14]. However, although small case series have suggested a potential role for the recombinant factor, at doses ranging from 10 to 90 μg/kg, for rapid warfarin reversal[15], no prospective, randomised studies have been conducted so far comparing the efficacy and safety of rFVIIa with either FFP or PCC for the reversal of warfarin-related acute bleeding. Although it is difficult to predict an individual's patient response, vitamin K can generally be given unless the patient is actively bleeding, because of the longer time required to reverse the over-anticoagulation[3,4]. There is general agreement that major or life-threatening bleeding requires rapid and complete warfarin reversal, which can be obtained only with FFP or PCC[16,17]. However, PCC have several advantages over FFP. First, various comparative studies have demonstrated that PCC are more effective than FFP at correcting International Normalised Ratio (INR)[3,18]. For example, in a study conducted by Makris and colleagues the mean post-treatment INR in patients receiving four units of FFP was 2.3 compared with 1.3 among patients receiving PCC at a dose of 25-50 IU/kg[19]. Furthermore, treatment was considered to have failed in all patients given FFP, because the lowest INR reported after FFP

therapy was 1.6. Likewise, in a study conducted by Cartmill and colleagues only one of the six patients receiving four units of FFP achieved a safe INR level below 1.5, compared with five of six patients receiving PCC at a dose of 50 IU/kg[20]. In this study, the mean correction time was shorter with PCC than with FFP (41 minutes *versus* 115 minutes). Two further studies showed that, compared with FFP, PCC were associated with significantly reduced clinical progression of intracerebral haemorrhage and greater and quicker (four to five times) reduction in INR[21,22]. These positive findings have been further supported by the very recent prospective multicentre study conducted by Imberti and colleagues on 92 patients with oral anticoagulant-induced intracranial haemorrhage treated with PCC at doses of 35-50 IU/kg[23]. A recent review by Leissinger and colleagues[24] of the published literature over the last 30 years identified 506 patients from 14 studies (7 prospective, 1 case-control and 6 retrospective studies) who received PCC for urgent warfarin reversal because of major bleeding or emergency surgery. Among the five studies in which PCC were compared with FFP, PCC were found to be more effective in shortening the time to INR correction. Thus, the authors concluded that PCC offer a rapid and specific method for replacing vitamin K-dependent clotting factors and restoring normal haemostasis in the context of over-anticoagulation.

Another major advantage of PCC over FFP is that smaller volumes of the former are required to reverse anticoagulation[25]. This is because the concentration of clotting factors in PCC is approximately 25 times higher than that in human plasma[3]. Thus, while FFP is often administered at doses of around 15 mL/kg, recommended doses of PCC required to achieve 50–100% levels of prothrombin complex factors can be delivered in injection volumes of 1-2 ml/kg. The reduced volume with PCC minimises the risk of fluid overload, especially in patients with a compromised cardiovascular system, and decreases the time needed for infusion. PCC are also quicker to prepare than FFP, as they can usually be stored at room temperature, allowing administration without warming, whereas FFP must be first thawed and then warmed[17]. In addition, PCC have a better safety profile than FFP because they undergo viral inactivation steps to minimise the risk of transmission of a variety of infective agents, including prions[17]. Another important consideration is the association of FFP with the risk of transfusion-related acute lung injury (TRALI), a major cause of death after transfusion[26]. This risk is not present with the use of PCC as the antibodies responsible for TRALI are removed during the manufacturing processes[17].

Based on the results of the clinical studies, several review articles and national guidelines currently recommend the use of PCC as primary treatment for rapid anticoagulant reversal in patients with life-threatening bleeding and increased INR[4,27-35]. Recently, Holland and colleagues showed that a PCC containing low amounts of FVII (a three-factor PCC) did not satisfactorily lower supra-therapeutic INR levels requiring plasma supplementation[36]. By contrast, several prospective studies conducted among patients requiring emergency surgery or experiencing major bleeding have documented that the four-factor PCC Beriplex P/N reverses warfarin anticoagulation rapidly, effectively and safely[37-42]. This PCC has also been found to be effective in controlling or preventing acute bleeds in patients with critical illnesses or severe liver disease involving deficiency of vitamin K-dependent coagulation factors[43,44]. Thus, in countries in which both three- and four-factor PCC are available, the latter is preferred, but when a four-factor product is not available it is advisable to use a three-factor product together with a small amount of FFP (as a source of FVII)[45].

Safety of prothrombin complex concentrates

Adverse events associated with PCC include immediate allergic reactions, heparin-induced thrombocytopenia (HIT, for the preparations containing heparin) and thromboembolic complications. The primary safety concern with PCC has been their association with thrombogenic events such as stroke, myocardial infarction, pulmonary embolism, disseminated intravascular coagulation and deep vein thrombosis[32]. In the review by Leissinger and colleagues[24], the PCC used for reversing warfarin anticoagulation were associated with a low risk of thrombotic adverse events (7/506 cases, 1.4%). These complications were thrombotic stroke (3 cases), deep vein thrombosis (2 cases) and non-Q-wave myocardial infarction (2 cases). Despite the apparent association of these events with PCC administration, in most cases

Table II - Thromboembolic complications with the use of the PCC Confidex

Author, year (reference)	Study design	Inclusion criteria	N. of patients	Thromboembolic events (%)
Evans, 2001 (37)	Prospective non-randomised	Major bleeding and INR > 14	10	0/10
Preston, 2002 (38)	Prospective non-randomised	Major bleeding or need for urgent reversal of anticoagulation	42	1/42 (2.4)
Lorenz, 2007 (39)	Prospective cohort	Need for urgent reversal of anticoagulation	8	0/8
Pabinger, 2008 (40)	Prospective multicentre	Emergency anticoagulation reversal	43	1/43 (2.3)
Bruce, 2008 (41)	Retrospective analysis	Severe bleeding	24	0/24
Schick, 2008 (42)	Retrospective	Major bleeding or urgent anticoagulation reversal	50	0/50
Staudinger, 1999 (43)	Prospective	Overt bleeding or planned invasive procedures in critically ill patients	16	0/16
Lorenz, 2003 (44)	Prospective multicentre	Acute bleeding or surgical/invasive procedures in patients with liver disease	22	0/22
Total			**165**	**2/215 (0.9)**

they could be attributed to the patients' underlying thrombotic risk factors. In addition, the already low incidence of such adverse events has further decreased over the last few years due to the improvement in the composition of the more recent commercially available PCC (i.e., inclusion of coagulation inhibitors, reduced use of activated coagulation factors, and improved balance of coagulation factors). In this context, Beriplex P/N, which contains a balanced concentration of the four vitamin K-dependent clotting factors and therapeutically effective concentrations of protein C and S, has proven efficacy and a reliable safety profile and thus represents the model of a modern PCC. Indeed, an analysis of published studies on the use of this PCC in different clinical situations (emergency reversal of anticoagulation, critically ill patients and patients with sever liver disease) showed a very low incidence of thrombotic complications (0.9%, see Table II), which compared favourably with data reported in the literature for other PCC. In addition, a recent prospective clinical trial from the Beriplex P/N Anticoagulation Reversal Study Group showed that this PCC can be rapidly infused (at a median of 7.2 mL/min; range 2-40 mL/min) for emergency reversal of coumarin therapy without altering its safety or effectiveness[46].

Conclusions

The literature data show that PCC are an important therapeutic option when urgent reversal of anticoagulation is required. Indeed, PCC not only correct clotting factor deficiencies more rapidly and completely than plasma, but are also associated with a lower incidence of volume overload and carry minimal risk of viral transmission. Finally, several prospective clinical trials have documented that PCC containing a balanced formulation of all vitamin K-dependent procoagulant and anticoagulant proteins have a high efficacy and safety profile.

Key words: prothrombin complex concentrate, PCC, thrombosis, over-anticoagulation reversal.

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