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REVIEW

Use of human protein C concentrates in the treatment of patients with severe congenital protein C deficiency

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Abstract: Protein C is one of the major inhibitors of the coagulation system that downregulate thrombin generation. Severe congenital protein C deficiency leads to a hypercoagulability state that usually presents at birth with purpura fulminans and/or severe venous and arterial thrombosis. Recurrent thrombotic events are commonly seen. From the 1990's, several virus-inactivated human protein C concentrates have been developed. These concentrates currently constitute the therapy of choice for the treatment and prevention of clinical manifestations of severe congenital protein C deficiency. This review summarizes the available information on the use of human protein C concentrates in patients with severe congenital protein C deficiency.

Keywords: Congenital protein C deficiency, protein C concentrate, purpura fulminans

Introduction

Protein C (PC) is a vitamin K-dependent coagulation inhibitor produced by hepatocytes. Plasma PC circulates as a 62-kDa-precursor serine protease that is activated by thrombin bound to a specific membrane protein, thrombomodulin. Together with its cofactor, protein S, activated PC specifically inhibits factor (F) Va and FVIIIa in a calcium and phospholipid-dependent manner, which in turn downregulates thrombin generation. Similar to all other vitamin K-dependent coagulation proteins, plasma concentration of circulating PC is significantly decreased at birth and during childhood at approximately 50% and 20% of adult values, respectively. This age-dependent decreased plasma concentration of PC is physiological and does not increase the thrombotic risk during childhood.[1]

Congenital PC deficiency is an autosomal dominant inherited disorder caused by mutations of the PC gene (*PROC*, OMIM #176860) located on chromosome 2q13–14. Thus far, 151 different mutations have been described.[2] Reported incidence of heterozygous PC deficiency varies between 1 in 200 to 1 in 500 healthy individuals. The incidence of homozygous PC deficiency is estimated at 1 in 500 000–750 000 of newborns, with an equal distribution between males and females.[3]

Congenital PC deficiency is associated with an increased risk of thromboembolic events. While heterozygous PC deficiency in adult patients is associated with a 10-fold increased risk of developing thromboembolic events compared to the general population, homozygous or double heterozygous PC deficiency represents a severe thromboembolic disorder. This usually manifests within hours of birth with life-threatening purpura fulminans (PF) and large-vessel thrombosis requiring urgent therapy including PC substitution.[4]

Until the end of the 1980's, no human PC concentrates were available. Patients with severe PC deficiency were treated with infusions of fresh frozen plasma (FFP) or

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cryoprecipitate.[5–12] Many of these patients died.[6,13] Following the introduction of commercially available human PC concentrates, several patients have been successfully treated and their cases are reported in the literature.[14]

This review will summarize the available information on the use of human PC concentrates to treat severe congenital PC deficiency.

Severe congenital protein C deficiency

Clinical presentation

While intrauterine and prenatal presentation (including arterial ischemic stroke and cerebral hemorrhage, thrombosis of the vitreal veins, and retinal arterial thrombosis and hemorrhage) has been reported, severe congenital PC deficiency usually presents immediately after birth with life-threatening PF and/or disseminated intravascular coagulation (DIC).[3,5–9,12] Purpura fulminans is an acute, progressive hemorrhagic necrosis of the skin caused by dermal vascular thrombosis. Lesions present initially as small ecchymoses that rapidly become purplish black with bullae, and then become necrotic and gangrenous.[15–16] Purpura fulminans may develop on the extremities, the buttocks, abdomen, scrotum, and scalp as well as at pressure points, previous punctures locations, and at previously affected sites.[4] Following the neonatal period, severe PC deficiency may cause further episodes of PF triggered by infection or trauma and recurrent venous thrombotic events including deep vein thrombosis (DVT) and pulmonary embolism (PE).[5,13]

In patients with homozygous PC deficiency but small detectable levels of PC, delayed clinical presentation including spontaneous large vessel thrombosis and skin necrosis following initiation of oral anticoagulation (OAC) therapy with a vitamin K antagonist is usually observed.[3,17–21]

Overview of treatment options

Treatment options for severe congenital PC deficiency include the substitution of PC or liver transplantation. In the early 1980's, PC was replaced by the administration of FFP and/or cryoprecipitate.[5–9] FFP consists of plasma separated from red cells and platelets by centrifugation of whole blood and frozen to –18°C within 6 hours of collection. One milliliter of FFP contains approximately one international unit of each of the coagulation factors and inhibitors. Cryoprecipitate is the precipitated plasma protein resulting from FFP thawed at 4°C, re-suspended in a minimal volume of residual supernatant plasma and subsequently refrozen at –18°C or lower. One bag of cryoprecipitate contains approximately 100 U of factor VIII, 880 U of von Willebrand factor, 250 mg of fibrinogen, and 50 U of factor XIII. Both concentrates require frequent plasma infusions once to twice daily to achieve significant improvement of symptoms, possibly leading to volume overload.[12–14] As well, both plasma products are associated with severe adverse effects.[5,6,9,13,22] Apart from the risk of infection, undesirable effects of FFP include allergic reactions, alloimmunization from contaminant red cells, and on rare occasions, pulmonary edema.[12,23–26] A major side effect of cryoprecipitate is passive transfer of isoagglutinins from the ABO blood group system due to the presence of plasma immunoglobulins.

Factor IX concentrate and PC-rich prothrombin-complex concentrate (PCC) have been successfully used in patients with severe congenital PC deficiency.[10–12] The concentration of PC in PCC showed an up to 10-fold variation in several brands, leading to a rise in plasma level of PC above 100 IU/dL with an approximately 7.4-hour half-life.

Following the development of human PC concentrates based on knowledge gained from the production of PCC in the 1970's, several virus-inactivated PC concentrates were developed in the 1990's. These currently constitute the treatment of choice for severe congenital PC deficiency. While a recombinant-activated PC concentrate (drotrecogin alfa, Xigris®) has been successfully administered on different occasions to treat episodes of PF in patients with severe congenital PC deficiency, the concern about an increased risk of major bleeding episodes in children may limit the use of this concentrate, at least in the pediatric population.[27–31]

A curative therapy for severe congenital PC deficiency is liver transplantation. Four patients who have undergone successful liver transplants have been reported so far. One child at 20 months and another at 6 months of age received elective living donor liver transplantation.[32–33] Angelis et al reported an additional girl, who received auxiliary liver and renal transplantation due to renal insufficiency following neonatal bilateral renal vein thrombosis.[34] The fourth successful liver transplant was reported in a 5-year-old boy who had previously been treated with long-term PC replacement therapy.[35] In all patients, PC activity was fully reconstituted.

Human protein C concentrates

Development of human protein C concentrates

The first production of human PC concentrates was based on the expertise gained from the production of PCC of Immuno AG in Vienna, Austria in the 1970's. The human PC concentrate, Ceprotin®, was developed in 1990 and first put on the market by Baxter Healthcare Corporation (Deerfield, IL, USA) in 1991. Ceprotin® was licensed in

Europe by the European Medicines Evaluation Agency in 2001 for patients with congenital PC deficiency and with complications of therapy with vitamin K antagonists. FDA approval of Ceprotin ® for severe congenital PC deficiency was obtained in 2007 (orphan drug status). The French human plasma-derived concentrate Protexel® (LFB, France) has been available since 1994.

Manufacturing of human protein C concentrates

As mentioned, two human PC concentrates are available for the treatment of severe congenital PC deficiency in Europe and North America: the human plasma preparation Ceprotin® (Baxter) and the French PC concentrate Protexel® (LFB, Les Ulis, France). Another, hence-activated human PC concentrate, Anact® (Kaketsuken, Kumamoto, Japan), is only available in Japan.

Ceprotin® is a sterile lyophilized human PC concentrate produced from frozen human plasma, collected in the United States or Europe. The cryoprecipitate is separated and the prothrombin-complex is isolated by DEAE-Sephadex, leading to a fraction of plasma, rich in factor VII, factor IX, protein S and PC. The product undergoes several washing steps using anion exchange chromatography and immunoaffinity chromatography on a murine monoclonal antibody against human PC. Two virus inactivation steps are performed by polysorbat 80 treatments and vapor heating (60°C for 10 hours and 80°C for 1 hour). Human albumin is added as a stabilizer before sterile filtration. The concentrate is negatively tested for HIV, hepatitis A, B, C and parvovirus B19. Activated PC and murine IgG are not detectable. Ceprotin® contains heparin and, potentially, mouse protein. The content of more than 200 mg sodium in daily maximum dosing has to be taken into account in patients with renal insufficiency. Both human PC concentrates contain the inactive PC zymogen, which is activated after infusion and allows controlling of PF and DIC in PC-deficient patients. The Ceprotin® solution has a specific PC activity of more than 200 IU/mg protein and can be administered directly as intravenous infusion. The administration of 1 IU human PC concentrate Ceprotin® leads to a median increase of plasma PC activity of 1.4%. Half-life is individually variable between 4.4 and 15.9 hours (median 10 to 12 hours). During acute PF or DIC, half-life can vary significantly due to ongoing consumption. Individual recovery also shows a wide range of 20.4% to 83.2% (median 68.5%).[36]

Protexel® is produced from human plasma donations by cryoprecipitation and undergoes three anion exchange chromatography and affinity chromatography purification steps. Virus inactivation steps are performed with 1% polysorbat 80 and 0.3% tri(N-butyl)phosphate, which effectively inactivates enveloped viruses. Protexel® yields a specific PC activity of more than 100 IU/mg total protein. Half-life ranges from 7.8 to 11 hours in adults in a stable situation, dependent on the acuity of the disease. Recovery is 1.58% (range 0.8 to 1.91%) per IU/kg injected.

Anact® is produced from human plasma collected from unpaid donors in Japan and activated by human thrombin, followed by further washing steps with ion exchange chromatography and monoclonal antibody separation as described by Katsuura.[37] Virus inactivation is performed by dry heat at 65°C for 10 hours and 15 nm nanofiltration. This concentrate is only available in Japan. Since there are only two case reports on the use of this activated human PC concentrate in the English literature, this concentrate will not be discussed further.[38–39]

Clinical use of human protein C concentrates

Reported cases on the clinical use of PC concentrates in patients with severe congenital PC deficiency are summarized in Table 1. Human PC concentrates have been successfully used for the treatment of acute PF, DIC, DVT, and coumarin-induced skin necrosis, as well as for prophylaxis to avoid relapse of acute symptoms, in the initial phase of OAC therapy, and during surgical procedures.

Use in acute clinical situations

Reports of 62 patients treated with human PC concentrate are available (Table 1). Forty patients were treated for typical neonatal manifestation, specifically PF in 36 of them. Intracerebral hemorrhage or infarction was present in 13 patients and eye complications, ie, vitreous hemorrhage and retinal arterial thrombosis and hemorrhage were present in 26 patients. Seven patients presented with coumarin-induced episodes of skin necrosis, three of them were adult patients, and four were children aged 8 to 16 years. Two patients were treated because of DVT. Only patients reported by Dreyfus et al[23] were treated with Protexel®, all other patients received Ceprotin® or the corresponding former PC concentrate, developed by Immuno AG, Vienna.[14,17–21,33,35,40–68]

In the vast majority of cases, treatment was initiated by replacement of FFP at doses of 10 to 15 mL/kg every

Table 1 Treatment reports of substitution with human protein C concentrates in patients with severe protein C deficiency

Reference #	Patient age	Clinical presentation	Dose of protein C concentrate*		Concomitant treatment	Outcome
			Acute therapy	Prophylactic therapy		
40	3 newborns	Intracranial hemorrhage, PF, eye involvement	60–80 IU/kg i.v. 6–8 h	108 IU/kg/d 306 U/kg/d s.c. over 1–12 h		No recurrence
41	newborn			550 IU/d, then 85 IU/kg i.v. 3x per wk	LMWH	No recurrence
	1 day	PF, intracranial hemorrhage, eye involvement	156 U/kg 12 h	90 IU/kg i.v. 3x per wk		Blind, developmental delay
42	5 (4 < 5 wk, 12 y)	PF, necrotic hematoma, DVT, surgery	Protexel® 125 ± 49 IU/kg/d i.v. (median 105 IU/kg/d)	Protexel® 24–90 U/kg/d i.v.	UFH, LMWH, OAC	Resolution, successful surgery
43	34 wk of gestation	PF, intracranial hemorrhage, infarction	80 IU/kg/d i.v.		UFH	No recurrence
44	22 y	Cesarian section		3000 IU i.v. once	LMWH	Successful
45	29 d	PF, eye involvement	80 U/kg i.v. 12 h	350 U/kg s.c. 48 h (pump), 192 U/kg/48 h	FFP	No recurrence, visual impairment
35	2 d	PF Recurrent PF on OAC	125 U/kg/d i.v. and s.c.	 75–66 IU/kg/d s.c.	LMWH	Resolution No recurrence
46	21 d	PF; eye involvement	50 U/kg i.v. 8 h, then 200 U/kg 12 h	250–350 U/kg s.c. 2 d	FFP + LMWH for 21 d	No recurrence, blind
	10 d	Periventricular infarction, eye involvement	50–100 U/kg i.v. 8 h	2000U s.c. 2 d		No recurrence, blind
47	15 d	PF Intracranial hemorrhage Initiation of OAC Shunt revision	100–200 IU/kg i.v. 6–8 h 200 IU/kg i.v. 12 h for 3 days	 200 IU/kg 12 h for 5 wk 200 IU/kg 12 h for 3 d	FFP 10–15 mL/kg every 12 h for 6 d OAC	Blind, neurological deficits
48	4 y	Initiation of OAC	63 IU/kg 12 h		OAC	Successful
17	8 y	Coumarin-induced skin necrosis	40 IU/kg/d for 8 d		OAC	No recurrence
49	7 mo	PF		500 IU/wk i.v.	OAC	No recurrence
50, 51	10 mo	Ventriculo-peritoneal shunt and vitrectomy		50 IU/kg i.v. every 12–48 h	LMWH	Successful surgery
	32 y	Thrombophlebitic episode Varikosectomy	50 IU/kg once, 40 IU/kg 24 h	40 IU/kg, then 15–20 IU/kg/d for 8 d	LMWH	Resolution, successful surgery
52	2 d	PF, eye involvement recurrent PF	Dose n.a. i.v. for 6 wk 100–125 IU/kg s.c., then 75 IU/kg/d 3–5 d	75 IU/kg/d s.c. (500 U/ml)	LMWH	Blind
53	25 mo	PF	Dose n.a.		FFP 5 mL/kg/d	No recurrence
54	36 wk of gestation	Intracranial hemorrhage, eye involvement	80 IU/kg i.v.			Resolution of macular hemorrhage, hydrocephalus

33	Newborn	Bilateral renal vein thrombosis	Dose n.a.	Dose n.a. 12 h	UFH, LMWH	Renal insufficiency
18	16 y	Coumarin-induced necrosis	80U/kg i.v.	80 IU/kg/d for 5 d	UFH, LMWH OAC	Resolution
55	4 y	PF	200 IU/kg i.v. 6 h for 2 days		LMWH OAC	Resolution
56	9 d	PF, cerebral infarction, eye involvement	20 IU/kg i.v. 6 h to 80 IU/kg i.v. 12 h	80 IU/kg i.v. 12 h to 2x per wk, 350 U/kg s.c. 48 h	OAC	Blind, hemiparesis
57	4 newborns	PF, cerebral infarction, eye involvement	Dose n.a. i.v.	250 IU/kg s.c. 3 d 100 IU/kg s.c.2x week 100 IU/kg/d s.c. 350 IU/kg 48 h s.c.		No recurrence in all patients
58	11 d	PF, eye involvement	Dose n.a.	Dose n.a.		Resolution, visual impairment
	9 d	PF/DIC, eye involvement	Dose n.a.		OAC	Resolution, visual impairment
59	10 d	PF, bilateral renal vein thrombosis	Dose n.a.			Improvement
19	9 y	DVT, recurrent coumarin-induced skin necrosis	40 IU/kg 18 h to 100 U/kg 24 h for 2 wk		Heparin OAC	Resolution
60	27 y	pregnancy and cesarean section		50 IU/kg 3x per wk 4th–13th wk and 35th wk to post-partum	OAC	Successful pregnancy and delivery
61	2.5 y	recurrent skin necrosis on OAC	100–200 IU i.v. 6 h	250 U/kg s.c. 3 d over 2 h (pump)		No recurrence
62	20 d	PF, eye involvement	70 IU/kg i.v. 6 h	500 IU/kg/d i.v.	OAC	Resolution, no recurrence
23	4 d	PF, eye involvement, surgery; recurrent PF	20 IU/kg i.v., then 40 IU/kg 6h;		OAC	Resolution
	3 mo	Dialysis, difficult OAC		20 IU/kg/d i.v., then 80 IU/kg/d	OAC	Renal failure
	2 d	PF, eye involvement, DIC	50 IU/kg i.v.	50 IU/kg 2x per wk	OAC	Blind
	20 d	PF, eye involvement	40 IU/kg i.v. 8 h	500 IU/d, 110 IU/kg 2x per week	OAC	Blind
	7 d	PF, eye involvement; recurrent PF	40 IU/kg i.v. 8 to 12 h	750 IU/d, then 1000 IU/d, then 3000 IU s.c. 3 d	OAC	Visual impairment
	4 d	PF	40–80 IU/kg i.v. 6 h	500–1000 IU/d		Resolution
	15 d	PF, eye involvement	120 IU/kg i.v. 8–12–24 h	500 IU/d	OAC	Blind
	5 d	PF, eye involvement; recurrent PF	80 IU/kg i.v. 6 h to 125 IU/kg 8 h		OAC	Blind, mild neurological deficits
	6 wk	PF, eye involvement, cerebral hemorrhage	70 IU/kg i.v. 6 h	30 IU/kg/d		Died

(*Continued*)

Table 1 (*Continued*)

Reference #	Patient age	Clinical presentation	Dose of protein C concentrate*		Concomitant treatment	Outcome
			Acute therapy	Prophylactic therapy		
63	2 d 24 h	PF PF, eye involvement	100–200 IU i.v. 6 h Dose n.a.	500–1000 IU/d i.v. Dose n.a.		Resolution, Resolution, blind
20	52 y	DVT, recurrent coumarin-induced skin necrosis	50 IU/kg 12 h i.v.	50 IU/kg 12 h i.v. for 10 days	LMWH warfarin	Resolution, no recurrence
64	2 d , 28 wk of gestation	PF, eye involvement PF, intracerebral hemorrhage, eye involvement	Dose n.a. i.v. 12 h		heparin <24 h	Blind Deceased at 23 d
65	2 d	PF, eye involvement	250 IU 6 h		FFP 15 ml/kg every 12 h, OAC	Resolution
21	58 y, 41 y	Recurrent DVT, recurrent coumarin-induced skin necrosis; Pharmacokinetic studies	80 IU/kg i.v.			
66	17 y	DVT, initiation of OAC	39 IU/kg i.v. 6 h, then 18 h for 4 d		Heparin i.v. 40000 IU/d for 5 d, OAC	Successful switch to OAC
67	7 y	Pharmacokinetic studies	40 U/kg i.v.		OAC	
14	Newborn	PF	20 to 40 IU/kg 6h i.v., at 14 d 30 IU/kg 12 h			Resolution
		Open heart surgery (VSD)		135 IU/kg i.v. once, 16 IU/kg continuous i.v. during surgery, then 60 IU/kg 6 h for 41 d, then 100 IU/kg/d i.v.		Successful surgery
		Catheter-related thrombosis of VCS		240 IU/kg/d for 3 wk	Heparin i.v. (30-50 IU/kg/h)	
68	10 mo	PF		Human protein C and S concentrate HT (Schwab+Co, Vienna): 100 U/kg PC every 48 h for >7 months		No recurrence

Notes: *Ceprotin® by Baxter or former human protein C preparation by Immuno AG; others indicated.

Abbreviations: PF, purpura fulminans; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; h, hour(s); d, day(s); wk, week(s); mo, month(s); y, year(s); OAC, oral anticoagulation; FFP, fresh frozen plasma; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin; n.a., not available.

6 to 12 hours (next to heparin, cryoprecipitate, tissue plasminogen activator and others), followed by substitution of human PC concentrate, as soon as diagnosis of severe PC deficiency was made and/or the product was available. To treat PF or DIC, the daily dose of human PC concentrate varied between 80 IU/kg in a single daily dose and 750 IU/kg in repeated doses (250 IU/kg every 6 hours) depending on the degree and resolution of clinical symptoms during treatment. In most cases the dosage of PC concentrate was titrated according to target PC activity levels of 100% and trough levels of 25%, or was adapted according to clinical stabilization, usually occurring after several days to weeks. Recurrent episodes of PF during OAC with vitamin K antagonists were treated with PC concentrate. Dosage of PC concentrate in these occasions ranged from 80 IU/kg once daily to 100–125 IU/kg as a first dose followed by repeated doses of 75 IU/kg to 200 IU/kg every 6 hours until resolution of lesions. Doses of PC concentrate in patients with DVT ranged from 40 IU/kg every 6 to 18 hours to 100 IU/kg once a day for 2 weeks. Patients with coumarin-induced skin necrosis were successfully treated with PC concentrate at doses of 80 IU/kg per day for several days and overlapping to the initiation of OAC.[18,20–21,44,68,69]

In general, patients with acute PF and/or DIC receiving PC concentrates in the early stage of the disease showed a much more favorable outcome than patients receiving PC concentrates after several days. However, early administration of PC concentrates in patients with intrauterine, intracerebral, or intraocular hemorrhage or infarction did not prevent long-term neurological complications or visual impairment. Few cases are reported where treatment with FFP or PC concentrate was too late to save the patient's life.[23,41,52,54,56,63–64]

General recommendations

No well-defined general dose guidelines are available for the treatment of symptomatic patients with severe congenital PC deficiency. However, available information from small case series and case reports suggests that the use of FFP or PC concentrates may positively influence long-term outcomes, especially when administered early in the disease. Based on this information, several recommendations have been published recently. The American College of Chest Physicians (ACCP) guidelines for antithrombotic therapy in symptomatic neonates and children recommend treatment with either 10 to 20 mL/kg FFP every 12 hours or PC concentrates at 20 to 60 IU/kg until resolution of clinical lesions.[70] Goldenberg and Manco-Johnson recommend a higher and more frequent dosage of PC concentrates consisting of an initial bolus of 100 U/kg followed by 50 U/kg every 6 hours or administration of 10 to15 mL/kg of FFP every 8 to12 hours until PC concentrate is made available.[71] Knoebl et al suggest the administration of PC concentrate as an initial intravenous dose of 60 to 80 U/kg followed by injections every 6 hours, especially during the acute phase.[36] Further dosage should be planned on an individual basis aiming at a PC activity of 100% (=100 U/dL) or a trough level of about 50 U/dL. The measurement of plasma PC activity before and after injection of PC is recommended in order to assess recovery and half-life, as both may be significantly reduced due to acute thrombotic events. Continuous infusions of PC concentrate seem to be efficient without loss of activity of PC. White et al recommend administration of a testing dose of 10 IU/kg of PC concentrate, followed by a bolus dose of 100 IU/kg, and a continuous infusion of 10 U/kg/h, adjusted to the measured PC activity and recovery.[72] Alternatively, subcutaneous administration of PC concentrate has also been described, especially for long-term treatment. In patients with coumarin-induced skin necrosis, the administration of heparin in therapeutic doses concomitant with intravenous PC concentrates is recommended.[71]

Prophylactic use

The goal of prophylactic administration of PC concentrates in patients with severe PC deficiency is to prevent relapse of acute disease, clinical manifestation during surgical procedures or pregnancy, and in the initial phase of OAC therapy.[14,18,20,23,33,40–42,44–47,49–52,56–58,60–63,68,75]

Prophylactic treatment is initiated after stabilization of clinical symptoms to allow an outpatient management (Table 1). In the patients reported, PC concentrate was individually reduced in dose and frequency from the therapeutic to a prophylactic level. Dose regimens of 24 to 90 IU/kg once a day, 250 to 350 IU/kg every other day, or 90 IU/kg three times a week were reported. Trough levels of PC above 15 to 25% as well as PC plasma level of 40 to 50% are thought to be sufficient to prevent relapse of PF or breakthrough skin necrosis. As an alternative to the intravenous route, several cases of subcutaneous administration of PC concentrate have been reported.[40,45–46,56,61] Subcutaneous doses of PC concentrate range between 66 to100 IU/kg once a day, 350 IU/kg every other day, and 250 IU/kg every third day. Duration of subcutaneous PC concentrate administration varies between 1 to 48 hours. For continuous subcutaneous PC infusion by pump, doses ranging from 192 to 350 IU/kg/48 hours are reported. Half-life of PC following intravenous and subcutaneous administration is 6 and 16 hours, respectively.[57]

Subcutaneous application is shown to be a reasonable alternative to the intravenous route, especially in the pediatric population as well as in long-term prophylactic treatment. However, long-term subcutaneous application can lead to subcutaneous fibrosis.[35]

Long-term OAC for prophylaxis was attempted at least once in almost all patients reported (Table 1). The switch from acute treatment with FFP or PC concentrate, at doses of 40 to 80 IU/kg/d or 200 to 500 IU/dose, to OAC was performed as early as after 5 days and up to several weeks or even years of PC substitution.[73] During long-term treatment with OAC as single agent, breakthrough PF and/or thrombotic complications were commonly seen in patients with severe PC deficiency. A successful combination of OAC with a target International Normalized Ratio (INR) of 1.5 to 2.5 and administration of PC concentrate at doses of 30 to 50 IU/kg every 1 to 3 days was reported in 8 patients.[71]

General recommendations

As above, no well-defined general dose guidelines are available for the prophylactic treatment of patients with severe congenital PC deficiency. In the ACCP guidelines for antithrombotic therapy in neonates and children, long-term treatment with PC concentrate replacement, next to treatment with long-term OAC, low-molecular-weight heparin, or liver transplantation is recommended. Administration of PC concentrate overlapping initiation of OAC, until an INR of 2.5 to 4.5 is achieved, has been suggested.[68,72–74] Heparin is thought to overcome the risk of coumarin-induced skin necrosis in the initial phase of OAC but no data are available to demonstrate this evidence.

For surgical interventions or invasive procedures, discontinuation of OAC and commencement of bridging using PC concentrate with an initial bolus of 100 U/kg followed by a maintenance dose of 30 to 50 IU/kg every 12 to 24 hours is recommended.[71]

Conclusions

Severe congenital PC deficiency is a serious disease, which usually becomes evident in the neonatal period with potentially lethal thrombotic manifestations. Early substitution of PC is crucial to stabilize consumption coagulopathy and allow resolution and healing of lesions. While the current source of available information does not allow general dose recommendations, data from case series and case reports suggest that purified human PC concentrates provide an adequate, safe, and efficient substitution of PC in acute situations as well as for prophylactic use in patients with severe congenital PC deficiency.

Disclosures

The authors report no conflicts of interest in this work.

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