Role of prothrombin complex concentrates in reversing warfarin anticoagulation: A review of the literature

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Over-anticoagulation is a common problem with warfarin therapy and can lead to major or life-threatening bleeding. The goal of urgent warfarin reversal is to elevate or replace vitamin K-dependent clotting factors. In the United States, fresh frozen plasma (FFP) is considered the standard of care for warfarin reversal. Prothrombin complex concentrates (PCCs) offer an alternative to FFP for rapidly replacing deficient clotting factors and correcting the international normalized ratio (INR). However, few prospective clinical trials have been conducted to evaluate the effectiveness of these concentrates relative to other treatment modalities. A review of the published literature over the last 30 years found that PCCs offer a rapid and specific method for replacing vitamin K-dependent clotting factors and restoring normal hemostasis in the context of over-coagulation. In those studies in which PCCs were compared with FFP, PCCs were found more effective in shortening the time to INR correction and were associated with a low risk of thrombotic adverse events. Evidence-based treatment guidelines are needed to optimize the use of PCCs for warfarin reversal. Am. J. Hematol. 83:137–143, 2008.   © 2007 Wiley-Liss, Inc.

Introduction

The coumarin derivative warfarin, which was licensed in the United States in 1954 as the first human anticoagulant [1], remains the most commonly used oral anticoagulant in North America and the United Kingdom [2,3]. Warfarin exerts its anticoagulant effect by acting as a vitamin K antagonist and inhibiting the biosynthesis of vitamin K-dependent procoagulant factors II, VII, IX, and X [2,4,5]. The maximum dose effect occurs up to 48 hr after administration of a single dose and persists for the next 5 days [6]. Warfarin overdose results from the administration of inappropriately high doses, altered protein binding, decreased vitamin K intake, reduced synthesis or increased clearance of vitamin K-dependent clotting factors, and the simultaneous use of other drugs (eg, erythromycin, fluconazole, amiodarone, propranalol, proxicam, and omeprazole) that compete with warfarin for protein binding [7].

Warfarin therapy is challenging because of substantial individual variations in dosage requirements that make over-anticoagulation common [2,8]. In addition, because warfarin has a narrow therapeutic window, treatment frequently results in bleeding, sometimes major or life-threatening [8]. Major bleeding, typically involving the gastrointestinal or urinary tracts or soft tissue, occurs in up to 6.5% of anticoagulated patients per year [9]. The incidence of fatal bleeding, primarily intracranial hemorrhage (ICH), is approximately 1% annually [9–13]. The risk of hemorrhage increases with the intensity of warfarin anticoagulation; the variable most consistently associated with bleeding risk is elevation of the international normalized ratio (INR), a standardized prothrombin time [2,3]. For most warfarin indications, the target maintenance INR is 2.0 to 3 [9,14]. However, the risk of bleeding is heightened even at low anticoagulation intensity (INR < 2.0) [12], and increases exponentially when the INR exceeds 5.0 [11,12].

The goal of urgent warfarin reversal is to elevate or replace vitamin K-dependent clotting factors [15]. The method used is determined by the INR and the clinical seriousness of the bleeding event [2,15]. Oral doses of vitamin K achieve partial reversal within 24 hr, whereas intravenous (IV) administration reverses anticoagulation within 4–8 hr [2,15]. High doses will not further shorten the time to anti-coagulation reversal but may lower INR more than is necessary and cause warfarin resistance that persists for up to 1 week [16].

There is general consensus that major or life-threatening bleeding requires rapid and complete warfarin reversal [2,17]. Fresh frozen plasma (FFP) is widely available and provides fast, partial reversal of the coagulopathy through the replacement of exogenous factors II, VII, IX, and X (FII, FVII, FIX, and FIX) [18]. FFP is considered the general standard of care in the United States, and although the optimal dose has not been established, FFP is most often administered in a dose of 15 mL/kg [19]. Volume overload may make it difficult to administer an adequate FFP dose, particularly since patients often have compromised cardiovascular systems [2,3,20]. FFP contains isohemagglutinins and must be blood group specific [21]. It also must be thawed before use, which can delay treatment, and infection transmission is a potential risk [3]. In patients with very high INRs who have profound decreases in vitamin K-dependent factors, replacement of hemostatic levels of these factors cannot be achieved with tolerable doses of FFP. Furthermore, the administration of FFP in recommended doses is often insufficient to normalize FIX levels [17].

Prothrombin complex concentrates (PCCs) provide a rapid and effective method for replacing deficient clotting factors and correcting INR. Taberner et al. first reported the successful use of PCCs to reverse over-anticoagulation in 1976 [22], and numerous reports from other investigators

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TABLE I. PCCs for Warfarin Reversal: Coagulation Factor Composition

	FII	FVII	FIX	FX	Indication on label
3-Factor PCCs					
Preconativ[a]	84 U	–	100 U	84 U	
Konyne[a]	152 U	16 U	100 U	152 U	
Factor IXa[a]	Unavailable	–	Unavailable	Unavailable	
Prothrombinex HT[b]	100 U	–	100 U	100 U	X
Bebulin[c]	120 U	13 U	100 U	139 U	
Profilnine SD[c]	148 U	11 U	100 U	64 U	
Cofact[d]	~75 U	~25 U	100 U	~75 U	
4-Factor PCCs					
Beriplex P[e]	128 U	68 U	100 U	152 U	
Prothromplex T[f]	100 U	85 U	100 U	100 U	X
Proplex T[a]	50 U	400 U	100 U	50 U	
Octaplex[d]	44–152 U	36–96 U	100 U	72–120 U	
PPSB-HT[g]	100 U	100 U	100 U	100 U	
Unknown					
Prothromplex[a]	Unavailable	Unavailable	Unavailable	Unavailable	

[a]No longer manufactured.
[b]Australia.
[c]US.
[d]UK and Europe.
[e]UK.
[f]Austria.
[g]Japan.

have followed. In many places, PCCs are the preferred method of urgent warfarin reversal [2,3,15]. PCCs are intermediate-purity pooled plasma products that were previously widely used in the treatment of hemophilia B prior to the availability of high-purity plasma-derived and recombinant FIX concentrates [2]. Of the PCC products used in studies pertaining to warfarin reversal (Table I), all contain factors II, IX, and X with variable amounts of FVII and natural anticoagulant proteins C and S [3,5].

Despite more than 30 years of reports detailing the efficacy of PCCs for rapid warfarin reversal, few prospective clinical trials have been performed to evaluate the efficacy of PCCs when compared with other commonly used treatment modalities. The purpose of this report is to review the published studies of PCC use for urgent warfarin reversal.

Results

Of the 14 published studies included in this review, only 3 were prospective, randomized, controlled trials [20,22,23], 4 were prospective, non-randomized studies [18,24,25], 1 was a case-controlled study [26], and the remainder were retrospective reviews [21,27–32]. All studies except one reported on subjects experiencing major bleeding or the need for surgery as the reason for urgent warfarin reversal; one study reported on the treatment of anticoagulant overdose without describing whether patients had symptomatic bleeding [22]. Three studies focused on the management of ICH or central nervous system (CNS) bleeding related to warfarin anticoagulation [20,26,28], and 10 studies described the treatment of major bleeding (not limited to ICH or CNS bleeding) in anticoagulated patients or the need for urgent warfarin reversal because of surgery or invasive medical procedures [18,21,23–25,27,29–31,33].

Reports demonstrating the efficacy of PCCs

Six reports described the efficacy of PCCs in restoring normal hemostasis in the context of over-anticoagulation. Several investigators closely followed laboratory studies to document reversal of prothrombin time or INR measure-

ments as an indication of hemostatic levels of vitamin K dependent factors. Three of these studies were prospective, nonrandomized treatment strategies. Evans et al. evaluated 10 patients with major bleeding linked to anticoagulation and found that a single PCC dose (30 U/kg) lowered the median INR from greater than 20–1.1 and achieved rapid hemostasis [18]. Similarly, Preston et al. found that PCC (25–50 U/kg) resulted in the immediate reversal of INR and an increase in vitamin K-dependent clotting factors and protein C in 42 patients [25]. Lubetsky et al., in a study of 20 patients with major bleeding or who required urgent surgery, reported that INR declined within 10 min following PCC injection (25–50 U/kg) [24]. A total of 85% of the patients had a good response to PCC reversal of anticoagulation (immediate cessation of bleeding), and the remainder had a moderate response (bleeding continued for 24–36 hr and required transfusions of packed cells).

In a retrospective review by Nitu et al. of 18 patients who required urgent reversal of anticoagulation, the mean INR before treatment exceeded 6.0 in 15 of 18 patients but dropped to 1.3 following a single PCC bolus (12–50 U/kg) [29].

Lankiewicz et al. retrospectively evaluated PCC in 58 warfarin-treated patients with acute bleeding or who required immediate surgery [21]. Within 1 hr of PCC administration (25–50 U/kg), the INR in all but 2 patients had corrected to less than 2, and their INRs had decreased to 1.5 or less in 44 patients (76%); the effect was maintained at 24 hr. Half of the patients also received FFP, and the results were similar to those receiving PCC alone, although 24-hr INRs were slightly higher with combination therapy. This observation led the authors to conclude that the acute INR correction with PCC, coupled with the subsequent impact of vitamin K administration, eliminates the need for FFP. Crawford and Augustson also questioned the addition of FFP to warfarin reversal with PCC in a retrospective review of 105 warfarin-treated patients who developed major or suspected bleeding or required surgery [27]. All patients with bleeding achieved hemostasis, regardless of whether they were treated with PCC alone ($n = 74$) or in combination with FFP ($n = 31$).

Studies comparing PCCs with vitamin K

In a prospective, randomized, controlled study, Taberner et al. described 18 patients treated with nicoumalone or warfarin randomized to receive either vitamin K (2.5 mg intravenously) or PCC (16 U/kg) [22]. Maximum correction occurred by 30 min after PCC injection, compared with 24 hr after IV vitamin K administration. Furthermore, vitamin K, even at a low dose of 2.5 mg, resulted in overcorrection in all patients given this treatment. Yasaka et al. prospectively compared vitamin K and PCC (7–27 U/kg) alone and in combination in 17 patients with major bleeding [33]. The INR significantly decreased ($P < 0.01$), and plasma levels of coagulation factors II, VII, IX, and X and protein C significantly increased ($P < 0.01$) 10 min after combination therapy. A similar reduction occurred after the administration of PCC alone, although the INR increased within 12–24 hr after injection. In patients treated with vitamin K alone, the INR decreased after 5–7 hr and dropped further after 12–24 hr.

Studies comparing PCCs with FFP

A randomized controlled study by Boulis et al. found that the rate of INR correction was significantly greater ($P < 0.01$) and the time to correction significantly shorter ($P < 0.01$) in patients with ICH treated with FFP plus PCC (40–50 U/kg; $n = 5$) versus FFP alone ($n = 8$) [20]. Although no difference in neurologic outcomes was noted between the 2 treatment groups, 5 of 8 patients who received FFP monotherapy had higher complication rates related to fluid overload. Cartmill et al., in a case-controlled study of 12 patients with ICH, also found that PCC (50 U/kg) achieved a significantly more rapid and complete INR reversal and correction than FFP ($P < 0.001$) [26].

In a retrospective review that compared PCC (average dose 25.8 U/kg) with FFP in 17 patients with ICH, Fredriksson et al. found that PCC was associated with a significantly shorter time to INR correction ($P < 0.001$) and significantly reduced the progression of ICH signs and symptoms compared with FFP ($P < 0.05$) [28]. Makris et al. conducted another retrospective review comparing the efficacy of PCC injection or FFP infusion in 41 patients with major bleeding attributable to or complicated by oral anticoagulants or who required urgent reversal of warfarin therapy [31]. Complete correction of the INR occurred within 15 min in 28 of 29 patients treated with PCC (50 U/kg) versus none of 12 patients given FFP.

Optimal PCC dosing studies

Some investigators have suggested that individualized PCC dosing may be a more rapid and cost-effective method of warfarin reversal [23]. In a prospective, randomized controlled trial that included 93 patients, 41 of 46 patients (89%) whose PCC dose was individualized based on initial INR, target INR, and bodyweight attained the target INR 15 min after PCC administration when compared with 20 of 47 (43%) patients treated with a standard PCC dose. As higher dosing of clotting factor concentrates may increase the risk of thromboembolic events [24,30], Yasaka et al. attempted to determine the optimal dose of PCC for the acute reversal of oral anticoagulation [30]. In their retrospective review of 42 patients, INR was measured before and 10–60 min after the administration of PCC (with or without vitamin K). INR was corrected in only 3 of 6 patients who received PCC at a dose of 200 U (assuming an average weight of 70 kg, this translates to an FIX dose of 3 IU/kg) but decreased rapidly and significantly ($P < 0.0001$) in 30 of 30 patients treated with PCC 500 U (FIX dose of 6 IU/kg). INR values in 6 patients receiving PCC 1,000–1,500 U (FIX dose of 14–21 IU/kg) also decreased,

and no thrombotic complications occurred in any of the patients. The researchers concluded that a PCC dose of 500 U (median 8.8 U/kg) may be optimal for emergent warfarin reversal in patients with an INR below 5.0, but that this dose may be inadequate in those with higher INR values.

Complications associated with PCC use

In these 14 studies that included 460 patients who received PCCs for warfarin reversal, there was no clinical evidence of disseminated intravascular coagulation (DIC), but 7 thrombotic complications occurred [21,23,25]. These adverse events (AEs) included a thrombotic stroke 48 hr after PCC treatment in a man who had severe sepsis and both cardiac and renal failure [25], 2 deep vein thromboses and 2 non-Q-wave myocardial infarctions that were not attributed to PCC therapy [21], and 2 patients with extensive comorbidities experienced nonbleeding strokes [23].

Table II summarizes the findings from these 14 studies.

Discussion

The last decade has seen a dramatic worldwide increase in the number of patients receiving long-term warfarin anticoagulation for the treatment of acute venous thromboembolism, the prevention of stroke in patients with atrial fibrillation, and the secondary prevention of myocardial infarction [31,34]. As new indications for anticoagulant therapy become established and the population ages, the use of warfarin and other anticoagulants is likely to further increase. Because of the narrow therapeutic range of warfarin, and the underlying bleeding risks in an aging population on anticoagulants, urgent warfarin reversal strategies that are effective and safe for a wide range of patients will be needed.

Historically, the guiding principle in urgent warfarin reversal has been rapid replacement of vitamin K-dependent factors using plasma infusions. The accessibility of FFP led to its use for this indication, but few studies were available to guide dosing, and observational studies suggested that complete warfarin reversal, as determined by laboratory values, often could not be accomplished with tolerable volumes of FFP. Nonetheless, clinical benefit generally was obtained, even with partial reversal of anticoagulant effect. This efficacy coupled with the near-universal availability of FFP in most countries resulted in its becoming a dominant strategy for urgent warfarin reversal.

As concentrates of vitamin K-dependent factors, PCCs appear to offer several advantages over FFP. PCCs provide more rapid and complete factor replacement, are infused in lower volume, and have enhanced safety because of viral inactivation. Consequently, numerous review articles and national guidelines now recommend the use of PCCs, rather than FFP, for rapid anticoagulant reversal [7,14,35] (Table III). Certainly, the studies reviewed here demonstrate that the hemostatic effects of warfarin can be completely and immediately reversed by a single PCC dose in the vast majority of patients. While this success rate is impressive, questions persist regarding the minimum effective dose and maximum safe dose. Confounding this issue is the wide array of PCC concentrates, all of which have variable proportions of factors II, X, and VII when compared with the FIX concentration, on which dosing is based. Seven of the 13 concentrates used in the studies described in this article contained very small or negligible amounts of FVII and were designated as 3-factor PCCs. Four of the studies reviewed used 3-factor PCCs without supplementing FVII, including 3 of the 4 studies that compared PCCs to FFP. Despite the lack of FVII, however, all studies with 3-factor

TABLE II. Summary of Studies that Evaluated PCCs for the Reversal of Anticoagulation

Author and study type	No. of patients	Reason for urgent warfarin reversal	Management	Outcome
Reports demonstrating the efficacy of PCCs				
Evans et al., 2001 [18], prospective nonrandomized	10	Major bleeding and INR > 14	PCC-4F*,a, dose: 30 U/kg	1. Median INR before treatment: >20 2. Median INR after single PCC dose: 1.1 3. Immediate cessation of bleeding at dose of 30 U/kg 4. No thromboembolic complications
Preston et al., 2002 [25], prospective nonrandomized	42	Major bleeding or need for urgent reversal of anticoagulation	PCC-4F*,a, dose: 25–50 U/kg	1. Immediate reversal of INR, vitamin K-dependent clotting factors, and protein C in all patients. 2. No clinical evidence of DIC; 1 thrombotic event
Lubetsky et al., 2004 [24], prospective nonrandomized	20	Major bleeding = 10 pts; urgent surgery = 10 Pts	PCC-4F*,b; dose: 25–50 U/kg	1. Rapid response (reduced INR within 10 minutes) rated "good" in 85% of pts, "moderate" in 15% of pts 2. Treatment was well tolerated
Nitu et al., 1998 [29], retrospective review	18	Major and minor bleeding or need for urgent reversal of anticoagulation	PCC-3Fc + FVII, PCC dose: 12–50 U/kg	1. INR before treatment: >6.0 in 15/18 pts 2. Mean INR after single PCC dose: 1.3 3. No thrombotic complications
Lankiewicz et al., 2006 [21], retrospectivereview	58	Major bleeding or need for urgent reversal of anticoagulation	PCC-4F*,d + FFP (N = 29), PCC dose: 25–50 U/kg	1. INR < 2 in 56/58 pts within 1H and sustained at 24H 2. 4 possible thrombotic events (likely linked to underlying medical conditions)
Crawford and Augustson, 2006 [27], retrospective review	105	Major or suspected bleeding or need for urgent reversal of anticoagulation	PCC-4Fe (N = 21), PCC-4Fe + Vitamin K* (N = 53), PCC-4Fe + FFP (N = 10), PCC-4Fe+ FFP + Vitamin K* (N = 21), PCC mean dose: 13 U/kg	1. All patients achieved hemostasis 2. No adverse effects reported
Studies comparing PCCs with vitamin K				
Taberner et al., 1976 [22], randomized controlled trial	18	Overdose	Vitamin K (N = 9), dose: 2.5 mg; PCC-4Ff (N = 9), dose: 4.7–16 U/kg	1. More rapid, controlled correction with PCC versus vitamin K 2. Overcorrection at 24 hr with vitamin K 3. No evidence of DIC with PCC
Yasaka et al., 2002 [33], prospective nonrandomized	17	Major bleeding [33]	Vitamin K* (N = 4), PCC-4Fg (N = 2), PCC-4Fg + Vitamin K* (N = 11), PCC dose: 7–27 U/ kg	1. INR significantly decreased (P < 0.01) and plasma levels of coagulation factors II, VII, IX, and X and protein C significantly increased (P < 0.01) 10 minutes after administration of PCC + vitamin K 2. INR decreased 10 min after administration of PCC alone but increased within 12–24 hr 3. INR decreased 5-7H after administration of vitamin K alone and decreased further after 12–24 hr
Studies comparing PCCs with FFP				
Boulis et al., 1999 [20], randomized controlled trial	13	ICH and PTT > 17 sec	FFP* (N = 8), FFP + PCC-3F*,h (N = 5), PCC dose: 40–50 U/kg	1. Rate of INR correction significantly greater (P < 0.01) and time to correction significantly shorter (P < 0.01) with FIX + FFP versus FFP alone.

TABLE II. Continued

Author and study type	No. of patients	Reason for urgent warfarin reversal	Management	Outcome
				2. No difference in neurologic outcomes 3. Higher complication rate (related to fluid overload) in FFP group
Cartmill et al., 2000 [26], case-controlled	12	ICH	FFP* ($N = 6$), PCC-3F*,i ($N = 6$), PCC dose: 50 U/kg	Significantly ($P < 0.001$) more rapid and complete INR reversal and correction with PCC versus FFP
Fredriksson et al., 1992 [28], retrospective review	17	ICH	FFP* ($N = 7$), PCC-3F*,j ($N = 10$), PCC mean dose: 25.8 U/kg	1. Significantly shorter time to INR correction ($P < 0.001$) with PCC vs FFP 2. Significantly reduced progression in ICH signs and symptoms ($P < 0.05$) in PCC-treated pts versus FFP group
Makris et al., 1997 [31], retrospective review	41	Major bleeding or need for urgent reversal of anticoagulation	FFP* ($N = 12$), PCC-3F*,e ($N = 29$), PCC dose: 25–50 U/kg	1. Complete correction of INR within 15 min in 28/29 pts treated with PCC versus 0/12 pts given FFP 2. Median post-treatment FIX level was 68.5 U/dL with PCC versus 19 U/dL with FFP 3. No thrombotic complications or clinical evidence of DIC
Optimal PCC dosing studies Van Aart et al., 2006 [23], randomized controlled trial	93	Major bleeding or need for urgent reversal of anticoagulation	PCC-3Fk ($N = 47$), dose ~7 U/kg, PCC-3Fk ($N = 46$), individualized dosing (~7–21 U/kg)	1. Significantly more patients treated with individualized dosing attained the target INR within 15 min of PCC administration compared with those given standard PCC doses 2. 2 thrombotic adverse events possibly linked to PCC administration
Yasaka et al., 2005 [30], retrospective review	42	Major bleeding or need for urgent reversal of anticoagulation	PCC-4Fl ($N = 11$), PCC-4Fl + Vitamin K* ($N = 31$), PCC dose: 200–1,500 U	1. PCC at a dose of 200 U reversed INR in only 3/6 pts and was judged inadequate 2. INR significantly decreased ($P < 0.0001$) in 30/30 pts 10 min following PCC administration at a dose of 500 U. 3. INR decreased in 6/6 pts following PCC administration at a dose of 1,000–1,500 U 4. No adverse effects noted

PCC-4F, 4-factor prothrombin complex concentrate; PCC-3F, 3-factor prothrombin complex concentrate; FFP, fresh frozen plasma; Pts, patients.
*Plus vitamin K 1–20 mg.
aBeriplex P/N (ZLB Behring; Marburg, Germany).
bOctaplex (Octapharma; Vienna, Austria).
cFactor IXa-BPL and Factor VII (Bio Products Laboratory; Herts, UK).
dProplex-T (Baxter; Deerfield, Illinois).
eFactor IXa-BPL plus Factor VII-BPL (before 1993; Bio Products Laboratory; Herts, UK) or Prothromplex T (after 1993; Immuno; Vienna, Austria).
fProthromplex (Immuno; Vienna, Austria).
gPPSB-HT Nichiyaku (Nihon Pharmaceutical; Tokyo, Japan).
hKonyne (Bayer; Elkhart, Indiana).
iFactor IXa-BPL (Bio Products Laboratory; Herts, UK).
jPreconativ (Kabi; Homburg, Germany).
kCofact (Sanquin; Amsterdam, The Netherlands).
lPPSB-HT Nichiyaku (Nihon Pharmaceutical; Tokyo, Japan).

PCCs reported rapid correction of laboratory values as well as improvement in clinical bleeding.

When compared with FFP, both 3-factor and 4-factor PCCs more rapidly and completely reversed laboratory markers of anticoagulation than vitamin K or FFP [20,22,26,28,31,33]. Only one comparison study was a prospective, randomized trial, and it included a small numbers of subjects presenting with ICH [20]. While laboratory reversal was clearly superior in the PCC arm, no difference was detected in neurologic outcomes. In another small retrospective study that compared FFP with PCC in patients presenting with ICH, both laboratory and clinical benefits were reported in the PCC group [28].

In studies comparing PCCs with FFP, no significant AEs occurred in the PCC group, but fluid overload was reported in the FFP group [20,31]. In reviewing AEs from all 14 studies, thrombotic events were reported in 5 of 308 patients who received 4-factor PCCs [21,25] and in 2 of 161 patients given 3-factor PCCs for warfarin reversal [23]. Although these studies suggest a low risk of thrombotic events associated with the use of PCCs for acute warfarin reversal, this risk is not negligible. Experience with PCCs in

TABLE III. Current Recommendations for the Use of PCCs for Warfarin Reversal

US 7th ACCP[a] Consensus Conference on Antithrombotic Therapy [35]
- PCCs or rFVIIa for serious or life-threatening bleeding at any INR elevation

UK Guidelines on Oral Anticoagulation [7]
- PCCs (50 IU/kg) for major bleeding

Australian Consensus Guidelines on Warfarin Reversal [14]
- PCCs for clinically significant bleeding, or
- PCCs for INR > 9 without bleeding

Italian Federation of Anticoagulation Clinics [36]
- PCCs for serious bleeding (e.g., CNS, gastrointestinal)

[a]American College of Clinical Pharmacy.

other patient groups have shown that thrombosis risk is related to the dose of PCC administered as well as underlying patient risk factors [23]. Since patients on warfarin therapy frequently have underlying venous and arterial thrombotic risk factors, studies are clearly needed to identify dosing strategies associated with the least thrombotic risk. One randomized prospective study looked at techniques for optimizing PCC dosing and concluded that clinicians should avoid overcorrecting the anticoagulant state, particularly in nonurgent clinical situations [23]. Of course, in critical or life-threatening bleeding, it is necessary to add vitamin K to PCC dosing for long-lasting reversal of anticoagulation.

Recombinant activated FVII (rFVIIa) has been proposed as another alternative for warfarin reversal [37–40]. Results from a few small case series indicate that bolus infusions of rFVIIa in doses ranging from 10 to 90 μg/kg rapidly reversed warfarin toxicity in patients with critically increased INRs [37] or warfarin-related ICH or CNS bleeds [38–40]. Optimal rFVIIa dosing in this clinical setting has yet to be determined. In addition, the short half-life of rFVIII (approximately 3 hr in adults) [41] may result in the need for multiple doses, if longer hemostasis is needed, which may increase the risk of thrombosis. [42] While rFVIIa can shorten and potentially correct an elevated INR without correcting the underlying deficiencies of factors II, IX, and X, a major concern is its ability to promote sustained, clinical hemostasis in the setting of very low levels of vitamin K-dependent factors. Furthermore, no prospective, randomized studies have been conducted comparing the efficacy and safety of rFVIIa with either FFP or PCC for reversal of warfarin effects and acute bleeding.

Methods

We conducted a search of the Medline database from January 1966 to July 2006 for English language articles pertaining to warfarin anticoagulation and anticoagulation/warfarin reversal (all methods). To avoid anecdotal reports and small case series, only studies that described at least 10 subjects were included in this review. Fourteen published studies that detailed the use of 13 different PCC products met the criteria [18,20–31,33]. Doses provided for the various PCCs studied refer to amount of FIX administered. Most of these products also contain varying quantities of factors II, VII, and X. In 7 of the PCC products studied, FVII was present in very small or negligible quantities (ie., <25% of the FIX concentration). These products are identified as 3-factor PCCs (PCC-3F). The other five PCC products contain appreciable levels of all four vitamin K-dependent factors and are identified as 4-factor PCCs (PCC-4F).

Table I shows the relative proportions of factors II, VII, and X, compared to FIX, contained in the products used in the cited studies.

Conclusion

While PCCs offer rapid and specific replacement of the depleted vitamin K-dependent factors, there is a pressing need for further evidence-based treatment guidelines to optimize therapy. Until such trials are accomplished, accumulating experience demonstrates that PCCs are superior to FFP for the urgent reversal of warfarin in patients with life-threatening hemorrhage, especially in patients with profound suppression of vitamin K-dependent factors. With the emergence of recent reports demonstrating the potential usefulness of rFVIIa in warfarin reversal, trials comparing efficacy and safety of PCCs and rFVIIa are needed.

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