Prothrombin complex concentrates for reversal of vitamin K antagonists: Assessing the risks

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Vitamin K antagonists (VKA) have been the standard for the treatment and prevention of thromboembolism in patients with atrial fibrillation, venous thromboembolism and prosthetic heart valves for more than 50 years. In 2004, more than 30 million prescriptions for warfarin were written in the United States (1). VKA are subject to significant diet- and drug-drug interactions; therefore, it is not surprising that warfarin is the most common cause of adverse drug reactions requiring treatment in emergency departments in the US (17.4%); more than 29,000 ED visits annually (1, 2). In 73% of cases, bleeding was the presenting problem, and 44% of patients required hospitalisation for its treatment (2).

Intracranial haemorrhage (ICH) is the most feared haemorrhagic complication of warfarin therapy occurring in 0.47% of patients annually (3). Warfarin-associated ICH has a case-fatality rate of 50%. Survivors often have residual neurologic deficits that result in significant functional disability (3). Since haematoma expansion is associated with poorer neurologic outcomes, rapid reversal of VKA therapy is essential. The traditional approach to vitamin K antagonist reversal is the intravenous administration of plasma and vitamin K. Although clinically rational, this approach is often cumbersome and slow (4). Intravenous vitamin K takes hours to reduce the international normalised ratio (INR). In one study of patients with a mean INR value of 12.7 (range 5.1–24.1), 66% of patients had an INR between 2 and 4 at 4 hours (h) and only 50% had an INR less than 2 at 24 h after 2 mg of intravenous vitamin K (5). Theoretically plasma should result in rapid INR correction, but the logistics of thawing and administering the large volume of plasma required introduces tremendous inefficiencies. In a retrospective review of 45 patients admitted to the Mayo Clinic for warfarin-associated ICH, Lee SB et al. found that it took an average of 30 h (range 14–49.5 h) and 5 units of plasma (± 2.1 units) for INR correction. The median time from presentation to plasma administration was 3 h (1.5–4.5 h). A median of 9.25 h (5–11.75 h) was required to complete plasma infusion (6). Goldstein et al. at the Massachusetts General Hospital noted similar delays and performance variation. A median of 90 minutes (min) (range 60–205 min) elapsed between presentation and administration of the first unit of fresh frozen plasma (FFP) in patients whose INR was less than 1.5 at 24 h. Among those who did not achieve an INR < 1.5 at 24 h, 210 min (range 100–375 min) elapsed before initiation of plasma (7). These experiences underscore the challenges and shortcomings of traditional approaches to reversal of VKA.

In 1997 Makris et al. compared the efficacy of two prothrombin complex concentrates (PCC) to plasma in 45 patients with warfarin-associated bleeds. In the 12 patients who received plasma the mean INR post-treatment was 2.3 (1.6–3.8) compared with 1.3 (0.9–3.8) in 29 patients treated with PCC. The median factor IX level was 19 units/dl (10–63 units/dl) and 68.5 units/dl (31–110 units/dl) for plasma and PCC, respectively. Similar differences were noted for other vitamin K-dependent coagulation factors. No disseminated intravascular coagulation was seen in PCC recipients. (8) Similar results have been noted in several smaller studies comparing plasma with PCC (9–11). The efficacy of PCC is also documented in a number of small case series, but no large randomised studies of plasma and PCC have been performed (4, 12–14). Although the experience has been largely positive, thromboembolic events have been noted which somewhat temper enthusiasm for PCC for VKA reversal (15, 16). The occurrence of thromboembolism is not entirely surprising since these patients were on VKA for management of thrombosis and would presumably be at higher risk for thrombotic events. However, the small size and clinical laboratory focus of many of the reports have made it difficult for providers to assess the risks of PCC for reversal of VKA.

In the current issue of Thrombosis and Haemostasis, Dentali et al. (17) attempt to address this knowledge deficit in their meta-analysis focusing on the safety of PCC in the reversal of VKA. Their search strategy identified 27 articles which were reviewed independently by two authors with disagreements adjudicated by the principal author. Studies were included if they used a PCC for rapid VKA reversal for bleeding or urgent/emergent surgery and included at least five patients. Studies of activated PCC were excluded. The PCC employed as well as the dose, indication for reversal and clinical adverse events (thromboembolism, death, viral transmission) were noted. Clinical outcomes were assessed using a random effects model given the potential for study heterogeneity. Three-factor and four-factor PCC were analysed separately. The 27 studies included 1,032 patients (6–261 patients per study). Fifteen studies were prospective and four enrolled consecutive patients. A total of 631 patients were treated for bleeding

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and 319 for urgent surgery. Twelve different PCC were used (7 four-factor and 5 three-factor PCC). Dosing varied but was usually based upon body weight and baseline and/or target INR. Fixed dosing was used in one study and bleeding severity or risk (with procedures) was also taken into account in three studies. Clinical judgment was used as well in one study. Vitamin K was given orally or intravenously in most studies and plasma was given in five studies as well as platelets and cryoprecipitate in one study. Follow up varied from seven days to six months. Thromboembolic events were uncommon affecting only 12 patients (1.4%); all occurred within a few (1–4) days of PCC administration. Ninety one deaths occurred. Thromboembolism occurred in 1.9% of patients treated for bleeding and 0.8% for patients treated for urgent surgery. Thromboembolism occurred in 1.8% of patients receiving four-factor PCC and 0.7% of patients receiving three-factor PCC. Seven studies assessed viral transmission; four patients (1.9%) became seropositive for parvovirus B19. No other infectious complications were noted. The total mortality rate was 10.6% (95% CI 5.9–16.6).

In summary, Dentali et al. have provided a useful estimate of adverse outcomes associated with PCC use for reversal of VKA. Their data indicate that PCC are relatively safe but are not risk-free. These data will allow clinicians to better determine which patients should receive PCC for warfarin reversal and caution against their indiscriminate use. These products should be reserved for patients taking a VKA who need urgent/emergent surgery or have serious life-threatening bleeding. Dentali et al.‘s meta-analysis also identifies outstanding clinical questions that need to be addressed including, the best product (3-factor vs. 4-factor PCC), optimal dose and comparative efficacy of PCC to traditional approaches to VKA reversal. The recent approval of new oral anticoagulants for thromboprophylaxis in atrial fibrillation and venous thromboembolism is changing the therapeutic landscape (18). Nevertheless, VKA likely will remain part of our treatment armamentarium for the foreseeable future. Therefore, randomised clinical trials enrolling patient populations with diverse thrombotic and haemorrhagic risk profiles will be relevant and important studies to perform in order to identify the optimal approach to the treatment of bleeding associated with VKA (19, 20).

Conflict of interest
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References