

Three or four factor prothrombin complex concentrate for emergency anticoagulation reversal?

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Patients on coumarin anticoagulants such as warfarin have reduced levels of functional coagulation factors II, VII, IX and X. Although highly efficient in reducing the risk of thrombosis, these drugs are associated with an increased risk of bleeding which is severe enough to require hospital admission in 1% per year and is fatal in 0.3% per year¹. In most patients with cerebral bleeding and in patients with gastrointestinal bleeding associated with haemodynamic instability, rapid anticoagulation correction is essential. As well as discontinuing the anticoagulant medication, agents that are commonly used in the reversal of the effect include vitamin K, fresh-frozen plasma, prothrombin complex concentrates and recombinant factor VIIa².

Temporary or permanent discontinuation of the anticoagulant is invariably required, but the long half life of the coumarin anticoagulants means that this measure alone is not going to have a major impact on the immediate situation¹. Vitamin K administration by the intravenous route has an effect as early as 6-8 hours³ and should always be administered to patients with major or life-threatening bleeding. Subcutaneous vitamin K results in inconsistent correction and the oral preparation produces a correction at 24 hours which is too slow for patients with life-threatening bleeding³. Although recombinant factor VIIa rapidly corrects the INR, its impact on stopping bleeding is unclear and its use is not recommended for warfarin reversal^{4,5}.

The main modes of emergency anticoagulation reversal in Europe are through the use of fresh-frozen plasma (FFP) or prothrombin complex concentrates (PCC). FFP contains normal levels of all the coagulation factors whilst PCCs contain factors II, IX and X with variable amounts of factor VII in a concentrated form. PCCs are virally inactivated and

can be given in a small volume without the need to thaw the product first. FFP however, has to be thawed before use, must be blood group specific and because it needs to be given at a dose of at least 10-15 mL/kg, it risks precipitating volume overload in the recipients who are often frail and elderly. Although guidelines often recommend PCCs over FFP because of their more rapid administration and complete INR correction⁶, it must be appreciated that there has never been a prospective randomised trial between the two products. Retrospective and in vitro data suggest that more complete correction of the coagulopathy is achieved with PCC than FFP^{7,8}.

All PCCs contain factors II, VII, IX, but some products contain no or very little FVII. PCCs with normal amounts of VII are known as 4-factor PCCs whilst the products without VII are 3-factor PCCs. Both types of product have been used in anticoagulation reversal and it is not known whether they differ in efficacy or safety. In a paper in the current issue of Blood Transfusion, Imberti and colleagues demonstrate the favourable efficacy and safety of a 3-factor PCC in reversing the anticoagulation of 46 patients with intracranial haemorrhage whilst on warfarin or acenocoumarol⁹. The median INR was 1.3 at 30 minutes post PCC infusion but more importantly clinical bleeding was arrested in all cases that it was possible to assess. There were no adverse events associated with the product during the hospital stay, but two patients experienced thrombotic events 47 and 56 days post administration. Nine of the 46 (20%) patients died from causes judged to be unrelated to the concentrate and although this may at first appear to be negative, it actually implies that the concentrate was given appropriately, i.e. to patients with truly life-threatening bleeding. Studies with virtually 100% survival should be interpreted with caution, because

it suggests that the cohort of patients recruited had less severe bleeding and could often have been managed with intravenous vitamin K alone.

The clear efficacy and safety of the 3-factor PCC used by Imberti and Colleagues in this study (Uman Complex DI®) is in stark contrast to the report of another 3-factor PCC (Profilnine SD®) by Holland *et al.*¹⁰. In their study Holland and colleagues used Profilnine SD and when given at a dose of 50 u/kg the median INR was only reduced from 8.6 (range 5.3-15.0) to 4.7 (range 1.4-15.0). Although the two products are different, their relative clotting factor composition is similar. For 100 units of FIX, the relative content of Uman Complex DI and Profilnine SD are respectively FII 100 and 150 units, FX 80 and 100 units and FVII 0 vs 35 units. The difference in response is therefore unlikely to be purely due to the clotting factor content of the two concentrates. The starkest difference between the two studies is the starting INR and this is the most likely explanation for the difference in reduction of the INR since the median starting INR was 3.5 in the Imberti study and 8.6 in the Holland report. There is a well-known inverse relationship between factor VII and INR, but this relationship is not linear and with INRs over 4.0-5.0 the level of FVII in patients is under 5-10%¹¹. Unlike other clotting factors, only 10-15% FVII is required for adequate haemostasis¹². It follows that whilst for the patients with relatively low INRs e.g. <4.5, there is sufficient FVII in the patient to allow 3-factor PCCs to be effective, for patients with significantly raised INRs the FVII is too low and adequate INR correction and anticoagulation reversal can only be achieved by a 4-factor PCCs. This is of course a supposition and ideally a prospective randomised trial between 3- and 4-factor PCCs in patients with a wide range of INRs is required to prove it. Consistent with this suggestion, however, are the stratified data of the Imberti study where the proportion of patients achieving an INR of <1.5 at 30 minutes were 89% for the group starting at 2.0-3.9, 33% in the 4.0-6.0 group and 0% in the patients over 6.0. In contrast to the experience with the 3-factor PCCs, 4-factor PCCs have been shown to be highly effective in reducing the INR and stopping bleeding in prospective studies irrespective of the starting INR^{13,14}.

The most feared complication associated with the

use of PCCs is thrombosis and although it has been suggested that this risk may be less with the 3 than the 4 factor PCCs, there is no evidence for this. The thrombotic risk is relatively low with both products but it must be appreciated that most studies report on efficacy rather than safety and when the latter is reported follow-up is very short. The choice of product is often dictated by the limited availability of licensed PCCs within specific countries.

The Imberti study is a welcome addition to the literature demonstrating the efficacy of a 3 factor PCC in patients with anticoagulant related intracranial haemorrhage. Until further information is provided about the use of this product in patients with higher INRs, its use in isolation should be restricted to the groups of patients largely included in the study, i.e. with INR of <4.0.

Conflicts of interest

Dr M Makris has received payment for providing consultancy to and lecturing at meeting sponsored by CSL Behring and NovoNordisk.

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