Prothrombin complex concentrate-related thrombotic risk following anticoagulation reversal

Peter Toth1; Mike Makris1,2
1Sheffield Haemophilia and Thrombosis Centre, Royal Hallamshire Hospital, Sheffield, UK; 2Department of Cardiovascular Science, University of Sheffield, Sheffield, UK

Dear Sirs,

We read with interest the report of the meta-analysis performed by Dentali et al. on the adverse events after prothrombin complex concentrate (PCC) use for the emergency reversal of vitamin K antagonists (1). The authors identified a low incidence of thrombotic events and a non-significant difference between four- and three-factor PCCs at 1.8% and 0.7%, respectively. We do not wish to criticise the meta-analysis itself, other than to say that we do not believe that this methodology is ideal to detect adverse events in observational studies and this limits the reliability of the estimates of the prothrombotic effects. Our concern is with the enormous variability in the studies included, especially with respect to:

a) The proportion of patients receiving PCC for emergency reversal of bleeding versus surgery.

b) The differences in starting INR, dose and type of PCC used.

c) The length of follow-up period during which adverse events were reported. The follow-up period was stated in only five of the 27 studies included which accounted for only 19% (200/1032) of the patients and in one study was as short as seven days (2).

Many of the studies included reported series designed to demonstrate the rapid correction in the international normalised ratio (INR) rather than to identify thrombotic events. Although prospective studies performed for regulatory purposes may theoretically be better in this respect, since the higher quality studies capture all events, the patients recruited are not always the same types of patients in whom these products are used in clinical practise. The main reason for this difference is that the time required to get informed consent, assess the entry criteria, and take baseline bloods introduces a delay and a selection bias that is not usually present when these products should be used clinically.

We are particularly concerned by one of the included studies which was published in abstract form in 2007 but has not been formally published in a peer-reviewed journal in the intervening four years. This important study contributed >25% (261/1,032) of the total number of patients to the meta-analysis but incredibly observed no deaths and no thrombosis (3).

Our clinical experience differs from this observation and suggests that the study may have used the PCC differently from usual practice.

We believe that the heterogeneity in the included studies was so high in terms of patients entered and length of follow-up, that the thrombotic risk estimates obtained by Dentali et al. must be considered as the minimal levels (1). Formal prospective studies of cohorts that include all treated patients followed for a sufficient period are required to establish the real thrombotic risk when these products are used for emergency reversal in the bleeding patient and those undergoing urgent surgery. We believe that when appropriately used, PCCs are the treatment of choice for the true emergency reversal of vitamin K antagonists and knowledge of the true thrombotic risk should discourage the unadvisable earlier use of these products.

Conflicts of interest

M. Makris has provided consultancy and has received honoraria for lecturing from CSL Behring. None of the other authors declares any conflict of interest.

References

