Three- or four-factor prothrombin complex concentrate for emergency anticoagulation reversal: what are we really looking for?

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Dear Sirs,

We read with great interest the excellent editorial by Makris and van Veen[1], which we believe contained some points that are worth further discussion. The authors comment on a well-performed study by Imberti *et al*. which showed the efficacy and safety of a three-factor prothrombin complex concentrate (PCC) for reversing warfarin anticoagulation in patients receiving oral anticogulation treatment[2]. In their conclusion, the authors stated that "*Until further information is provided about the use of this product in patients with higher INR, its use in isolation should be restricted to the groups of patients largely included in the study, i.e. with an INR of <4.0"*[1].

We would tend to attenuate this statement because, in our opinion, the real conclusion depends on what we are looking for, that is, the end-point that is chosen. If the goal is a better and faster normalisation of the International Normalised Ratio (INR), even for patients with extremely high INR values, a four-components PCC is probably better, since it is well known that the result of the INR test strongly depends on factor VII content. However, it is also well known that available tests, particularly the INR, are not able to provide a true picture of how the haemostatic system actually works. It should, therefore, always be kept in mind that, in studies on patients taking oral anticoagulants who have major and/or intracranial bleeding, INR normalisation is just a surrogate end-point. As a consequence we think that great care should be taken before translating biochemical data into clinical recommendations, even if expressed softly, as Makris and van Veen did. We do not have any evidence from available (and methodologically poor) studies of a greater efficacy on strong clinical end-points of four-factor PCC compared to three-factor ones. The argument for four-factor PCC, i.e. better and faster normalisation of extremely high INR, is non-clinical, and it could be counterbalanced by data showing greater safety of the three-factors PCC[3]: neither of which is so far supported by strong evidence from methodologically robust, published studies. A large, randomised trial comparing three- and four-factor PCC for anticoagulation reversal is advisable, but unrealistic. However, even small studies, provided that they are well conducted in carefully selected populations, such as trauma patients, can give some useful information on this relevant topic.

While awaiting for any better evidence, we should be very cautious about recommending one product with respect to another. Our goal should be to improve the overall use of PCC, since the literature clearly shows their dramatic underuse in life-threatening bleeding related to oral anticoagulation treatment[4], and the cost of the product could also be a relevant issue to be considered.

References

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Received: 21 February 2011 – Accepted: 7 April 2011
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