Reverse engineering for new oral anticoagulants: Non-specific reversal agents and the anticoagulant activity of dabigatran and rivaroxaban

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Anticoagulant agents are frequently used for prevention and treatment of a wide range of cardiovascular diseases. In recent years a large number of new antithrombotic agents have been developed and tested in clinical trials and many of these new agents are becoming widely available for clinical practice (1, 2). Main advantages of these new agents are the relatively stable pharmacokinetic and pharmacodynamic properties, which obviates the need for repeated control of the intensity of anticoagulation and dose-adjustments, and in some situations a better efficacy and safety as compared with conventional antithrombotic agents (1).

The most important complication of treatment with anticoagulants, old or new, is haemorrhage, which may be serious, may cause long-term debilitating disease, or may even be life-threatening (3). If severe bleeding occurs or if a patient needs to undergo an urgent invasive procedure, such as emergency surgery, it may be required to reverse the anticoagulant effect of the various agents (4, 5). In view of the relatively short half-life of many new anticoagulants, cessation of administration will be sufficient to normalise haemostasis in about 24 hours. However, in some situations a more rapid correction of coagulation is warranted. Depending on the clinical situation, i.e. the severity of the bleeding or the urgency and estimated risk of the invasive procedure, this reversal may have to take place in a few hours, and in some cases immediately (6, 7).

For most of the new anticoagulant agents no direct antidotes are available. However, a variety of non-specific prohaemostatic agents, currently used in clinical practice, may be effective to reverse the anticoagulant effect (8). For this indication most widely studied agents include (activated) prothrombin complex concentrates (PCC) and recombinant factor VIIa. Initial studies focused on the effects of various anticoagulants and various prohaemostatic agents on thrombin generation in vitro systems (9).

In this issue of *Thrombosis and Haemostasis* Marlu et al. take this topic a step further by presenting comprehensive data on the effect of different prohaemostatic interventions on thrombin generation asayed in blood from healthy volunteers treated with either rivaroxaban or dabigatran (10). They demonstrate that PCC’s correct rivaroxaban-induced impaired thrombin generation in a dose-dependent fashion. The effect of PCC on reduced thrombin generation after administration of dabigatran was less pronounced. In this situation, however, activated PCC and recombinant factor (F)VIIa had some, albeit relatively modest, effect. Based on these experiments the authors conclude that non-specific reversal agents seem to be capable of reversing the anticoagulant effect of the new oral anti-FXa and anti-FIIa agents.

The experiments presented by Marlu et al. are important and confirm the notion that non-specific prohaemostatic agents may be helpful in reversing the anticoagulant effect of new antithrombotic agents in case of severe haemorrhage or the need to perform an emergency invasive procedure. A similar picture emerges from animal experiments to evaluate the reversing potential of prohaemostatic interventions after the use of new anticoagulant agents (11, 12). An additional advantage of these models is that the effect of the prohaemostatic agents is not limited to laboratory observations, such as measurement of thrombin generation and other coagulation parameters, but that the effect on experimental bleeding can be evaluated as well. In most cases both (activated) PCC’s and recombinant FVIIa seem to be able to reduce blood loss in these models, in particular after the use of the anti-FXa agents. In addition, high dose PCC was effective in reducing experimental intracerebral haemorrhage induced by dabigatran (13). A randomised controlled *in vivo* human study in healthy volunteers demonstrated that administration of PCC resulted in a virtually complete correction of coagulation after intake of rivaroxaban, but not after intake of dabigatran (14). Since in this study only one dose of PCC was studied it may be that different dosing schemes may show efficacy for dabigatran reversal as well, and this will be subject of further study.

Despite this accumulating evidence that these non-specific prohaemostatic agents are capable of reversing the anticoagulant effect of new anticoagulant agents, the ‘proof of the pudding’ will be their efficacy in the clinical setting. Apart from anecdotal experience, there is no firm evidence that these agents will indeed reduce blood loss and improve outcome in patients with anticoagulant-induced bleeding, and it will be very difficult to design clinical trials to systematically address this issue. In the absence of this information and in the likely situation that the new anticoagulant agents will be much more widely used in the coming years, it is important to adequately document responses of bleeding patients to these interventions, for example by means of registries.

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The mechanism by which non-specific prohaemostatic agents reverse the anticoagulant effect of the anti-FXa and anti-FIIa agents is not completely clear and this may also be an area of further investigation. The findings of Marlu et al. and others demonstrate that both (activated) PCC and FVIIa are effective in case of FXa inhibition (10, 15). FVIIa is less effective in the reversal of thrombin inhibition but activated PCC’s and high dose PCC seem to have some effect (13, 16). Hence, it is less likely that FVIIa in (activated) PCC is the factor that drives the effect. Hypothetically, the relatively high concentration of coagulation factors and/or the combination of factors in (activated) PCC may be crucial for its effect in reversing anticoagulation.

In conclusion, despite the absence of a specific antidote the potential availability of non-specific reversing agents in case anticoagulant treatment with new anti-FXa or anti-FIIa agents is complicated by severe haemorrhage or in case of the need for immediate reversal, is promising and reflects current advice on managing this situation (17). When confirmed in clinical practice this option to reverse the anticoagulant effect will take away a potential barrier for widespread use of these new agents to prevent or treat thromboembolic disease.

Conflicts of interest
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