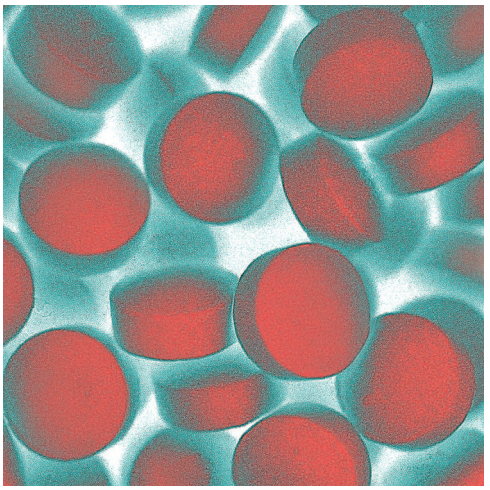
Novel Oral Anticoagulants

New Challenges for Anesthesiologists in Bleeding Patients

IN recent years, tremendous efforts have been made to develop new oral anticoagulants for the prevention of venous thromboembolism after surgery and in medically ill patients, prevention of stroke in atrial fibrillation, reduction of cardiovascular events in patients with acute coronary syndrome, and treatment of confirmed acute pulmonary embolism and deep venous thrombosis. The most prominent modes of action by these novel drugs are direct factor Xa inhibition (rivaroxaban and apixaban) or thrombin inhibition (dabigatran). These drugs are administered orally at fixed doses, and no monitoring is necessary compared with prothrombin time (PT)/international normalized ratio measurement in patients treated with oral vitamin K antagonists.[1]

Dabigatran received approval by the Food and Drug Administration (for the prevention of stroke in patients with atrial fibrillation) as of October 1, 2010[2] and rivaroxaban (for the prevention of venous thromboembolism after hip and knee arthroplasty[3–6]) as of July 1, 2011.

As is the case with all anticoagulants, including (low–molecular-weight) heparins and vitamin K antagonists, the new substances have an inherent bleeding risk.[1] When these novel anticoagulants are used for thromboprophylaxis after hip or knee arthroplasty (and thus for 2–6 weeks at low dose), the risk of major bleeding in such patients is low. However, new indications for these novel anticoagulants may arise with higher doses and longer treatment durations. Thus, anesthesiologists are likely to increasingly face patients who have experienced trauma or other causes of bleeding and who are being treated with these new anticoagulants. The most pertinent questions for which we do not yet have complete answers are: How can we measure the effect on blood coagulation? and How can we specifically treat such patients?



"… anesthesiologists are likely to increasingly face patients who have experienced trauma or other causes of bleeding and who are being treated with these new anticoagulants."

The study by Godier *et al.* in this issue of ANESTHESIOLOGY[7] is very important because it is the first that addresses these questions for rivaroxaban, which is now marketed in more than 100 countries. This study in rabbits was designed and executed elegantly: first, a dose-finding study was performed to find the necessary dose of intravenous rivaroxaban that would result in increased bleeding after a standardized liver and spleen incision. Consequently, the lowest rivaroxaban dose (5 mg/kg) was used in the main experiment, in which this dose was given in conjunction with saline, activated recombinant factor VII (rFVIIa, 150 μg/kg) or prothrombin complex concentrate (PCC, 40 units/kg), and the effects on traditional coagulation tests (PT and activated partial thromboplastin time), bleeding time, rotational thrombelastography, thrombin generation, and bleeding caused by a standardized liver and spleen incision were assessed. The attempt to measure "clinical" bleeding in this setting is a true and important novelty because previous studies were limited to *in vitro* coagulation assays and bleeding time. The three main findings of the study by Godier *et al.*[7] were (1) with the exception of the maximum clot firmness in rotational thrombelastography, all coagulation tests became clearly pathologic and bleeding caused by the standardized liver and spleen incision increased in rivaroxaban-treated rabbits compared with control animals; (2) the addition of rFVIIa and PCC partially normalized most coagulation test results; and (3) neither rFVIIa nor

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PCC reduced bleeding caused by the standardized liver and spleen incision in rabbits treated with high-dose rivaroxaban.

Rivaroxaban has a distinct effect on the results of most clinically used coagulation tests, including a significant prolongation of PT and activated thromboplastin time and thus a reduction of (functional) single-factor measurements performed in one of these test systems. Notably, these changes were measured after administration of only 10 mg rivaroxaban.[8] In contrast, thrombin time, fibrinogen, factor XIII, and D-Dimers are not affected.[8] The magnitude of this effect depends on the dose and time since the last rivaroxaban ingestion.[9] In addition, thromboelastometry parameters are dose-dependently affected by rivaroxaban.[10] The alterations in coagulation test results found by Godier *et al.*[7] are similar. However, all these changes are not specific for rivaroxaban and thus are of limited value in the treatment of patients with acute bleeding. In contrast, in the absence of (low–molecular-weight) heparin, measuring anti-Xa activity might aid clinicians in deciding whether or not there is a rivaroxaban effect. Very low anti-Xa activity (*e.g.*, <0.1 U/ml when using standard anti-Xa assays) suggests that there is no relevant rivaroxaban effect, whereas greater values suggest such an effect without directly quantifying it.

When evaluating the findings in the study of Godier *et al.*,[7] we need to keep in mind that the dose used in this animal model would be considered a massive *overdose* of rivaroxaban in the clinical setting. The authors first established the minimum dose of rivaroxaban necessary to induce a clinical coagulopathy with increased bleeding caused by a standardized liver and spleen incision. The dose established and used for additional experiments was 5 mg/kg, which is 8–10 times greater than the highest daily dose used in any of the clinical (human) phase 3 trials. In contrast, the doses of rFVIIa and PCC were fixed, and both were in the high-normal range of clinically used doses. Therefore the inefficacy of both treatments in reducing the bleeding associated with a standardized liver and spleen incision may reflect a relative under-dosing of rFVIIa in PCC in this study.

The findings on reversing the anticoagulant effect of rivaroxaban in the study of Godier *et al.*[7] are largely in keeping with the results of previous studies. Perzborn *et al.* showed that rFVIIa partially restored thrombin generation in human platelet-rich plasma because higher doses of rivaroxaban were necessary for the same amount of thrombin inhibition if rFVIIa was present (as presented at the 21st Congress of the International Society on Thrombosis and Hemostasis, Oxford, United Kingdom, August 2007). In rats treated with 2 mg/kg rivaroxaban, Tinel *et al.* found that a supratherapeutic dose of rFVIIa (400 μg/kg) partially normalized PT and thrombin generation (as presented at the 21st Congress of the International Society on Thrombosis and Hemostasis, Oxford, United Kingdom, August 2007). Finally, in baboons given 0.9 mg/kg rivaroxaban, Gruber *et al.*[11] found that 210 μg/kg rFVIIa shortened bleeding time and PT by approximately 30%. Thus, we may speculate that rFVIIa may help to mitigate bleeding in patients treated with rivaroxaban outside the context of rivaroxaban overdose. The following seem reasonable hypotheses: the use of rFVIIa induces direct activation of FX to FXa, where the amount of FXa generated seems linear to the amount of rFVIIa[12]; thus, in the presence of a given amount of a FXa inhibitor, the balance is shifted toward more available FXa and thus more thrombin generation, leading to increased soluble fibrin generation and increased cross-linking of fibrin monomers. In addition, an enhanced thrombin generation through the use of rFVIIa may increase platelet adhesion even in the presence of platelet defects.[13] However, it must be recognized that these hypotheses have been generated from *in vitro* models.

Similarly, high-dose PCC (50 U/kg) partially normalized bleeding time and PT in rats treated with rivaroxaban (2 mg/kg), whereas low-dose PCC (25 U/kg) was ineffective.[14] PCC is known to increase prothrombin conversion in addition to increasing factor concentrations through supplementation,[15] although the exact mechanism behind this observation remains to be elucidated. The most important possibilities are replenishment of relatively deficient coagulation factors in an environment of an activated coagulation system and additional coagulation activation through already activated coagulation factors possibly present in the concentrate. In a study in volunteers given 20 mg rivaroxaban twice daily for 2.5 days, PCC (50 U/kg) immediately and completely normalized PT and the endogenous thrombin potential.[16] This observation in humans is particularly important because the reversal potential of PCC was assessed in the high clinical dosing range of rivaroxaban. However, only the effect on PT and the endogenous thrombin potential were studied, not the direct effect on bleeding.

In conclusion, the study by Godier *et al.*[7] is important because it allows hypothesizing that procoagulants such as PCC and rFVIIa may help to correct the coagulopathy in patients treated with factor Xa antagonists. However, the study was performed in the context of overdosing: the administration of procoagulants partially corrected coagulation test results but did not reduce bleeding caused by the standardized liver and spleen incision in an animal model. Thus, additional studies similar to the one by Godier *et al.*[7] using rivaroxaban doses close to the ones used in the clinical setting are necessary to guide clinicians on how to specifically treat patients who have received novel anticoagulants.

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