Procoagulants for management of bleeding with the new oral anticoagulants

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Treatment guidelines give preference to new oral anticoagulants (NOACs) over warfarin for stroke prevention in patients with non-valvular atrial fibrillation (AF) because the NOACs are at least as effective as warfarin, but are associated with less life-threatening bleeding and do not require coagulation monitoring. Despite this endorsement, some clinicians are concerned about the lack of an antidote to reverse the anticoagulant effect of NOACs in patients who are bleeding or require urgent surgery.

To begin to address this concern, Perzborn et al. demonstrate that prothrombin complex concentrate (PCC) and recombinant factor VIIa (rfVIIa) favourably modify coagulation tests and the bleeding time (BT) in rats and baboons given therapeutic and supra-therapeutic doses of rivaroxaban (1). PCC shortened the BT to a greater extent than rfVIIa and the BT returned to normal, albeit transiently, in rivaroxaban-treated baboons given activated PCC. Despite correction of the BT, however, the prothrombin time (PT) remained prolonged, suggesting that procoagulants may attenuate bleeding, but fail to normalise tests of coagulation.

The failure of PCC to normalise the PT is at odds with the observation that PCC restores the PT to baseline levels in rivaroxaban-treated human volunteers (2). In contrast, the finding that PCC shortens the BT more than rfVIIa is consistent with previous results in mouse and rabbit models of rivaroxaban-induced bleeding (3, 4). Although case reports suggest that PCC and rfVIIa may attenuate bleeding in patients taking NOACs, clinical experience with these agents is limited.

Specific antidotes for NOACs are under development, but are several years away from approval. Should the absence of an antidote deter clinicians from using NOACs? We think not because population data suggest that rates of major bleeding with NOACs in the real world are similar to those reported in clinical trials (5), and secondary analyses of data from these trials indicate that the outcome of patients with major bleeds is no worse with NOACs than with warfarin. Therefore, we believe that the many advantages of NOACs over warfarin should prompt their use in appropriate patients. If bleeding occurs, holding the drug, local measures to stop bleeding and transfusion support are likely to be adequate in most cases (6). Although confirmatory human data are lacking, the work of Perzborn et al. provides additional support for the potential utility of procoagulants in patients with life-threatening bleeds.

Conflicts of interest

J. Eikelboom has received consulting fees and/or honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo, Pfizer, Merck, and Janssen Pharmaceuticals.

References