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In Reply to 'Idarucizumab Dosing in Kidney Failure'

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LETTERS TO THE EDITOR

Idarucizumab Dosing in Kidney Failure

To the Editor:

In the case report by Novak et al,[1] their use of a single idarucizumab dose and blood product therapy merits further discussion. We believe that idarucizumab dosing should be based on serial clinical assessments (eg, vital signs, hemorrhage site, and patient's response to therapy) and a profile of clotting times at least every 6 to 8 hours (eg, ecarin clotting time, thrombin clotting time, activated clotting time, and activated partial thromboplastin time) in addition to blood component therapy, as in the clinical scenario described by Novak et al.

Dabigatran is redistributed from peripheral tissues into the intravascular compartment following idarucizumab therapy.[1-4] Resurgence of dabigatran activity occurs after about 6 to 8 hours in patients with acute kidney injury or kidney failure.[1-3] Dabigatran does not discriminate between endogenous or exogenous sources of thrombin. Thrombin derived from blood component therapy (eg, prothrombin complex concentrate, activated prothrombin complex concentrate, or fresh frozen plasma) will be inhibited unless dabigatran activity has been neutralized. This suggests that the effectiveness of therapy should be assessed by serial clinical assessments and a profile of clotting times at least every 6 to 8 hours, with additional blood component and idarucizumab therapy as clinically indicated. In the REVERSE-AD study, 1.8% of patients received 10 to 15 g of idarucizumab,[4] while its product label indicates an additional 5-g dose of idarucizumab may be considered.[5]

The data for nonspecific prohemostatic agents are methodologically limited, but it is reasonable to administer blood component therapy to a patient with serious hemorrhaging due to excessive dabigatran activity based on in vitro and preclinical data.[6] Although the discrepancies between some of the animal data and data for humans may be due to different measured end points, these data suggest prothrombin complex concentrate and activated prothrombin complex concentrate to be more effective than fresh frozen plasma.[6] In select patients, the need to establish effective hemostasis using blood component and idarucizumab therapy outweighs the potential risk for thrombotic adverse events in patients who are hemorrhaging.

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In Reply to 'Idarucizumab Dosing in Kidney Failure'

We thank Drs Yip and Deng[1] for their insights on our case report.[2] We agree that frequent clinical and laboratory assessment in a patient with life-threatening hemorrhage is essential. Clinical examination of this critically ill patient was constant, and coagulation parameters were measured 10 times during his 3-day hospital course (approximately every 4 hours). We also agree that repeat dosing of idarucizumab may have been beneficial had it been possible, as in the report we cited of dabigatran toxicity in acute kidney injury (AKI).

The administration of prothrombin complex concentrates (PCCs) to reverse bleeding in patients with end-stage liver disease (ESLD) has not been rigorously investigated. Drs Yip and Deng note that PCCs attenuated hemorrhage in mice receiving dabigatran, but a recent report suggests that PCCs may have worsened bleeding in a patient with ESLD.[3] In that report, as in our case, the patient developed coagulopathy and AKI requiring hemodialysis catheter insertion. PCC administration resulted in disseminated intravascular coagulation, with epistaxis, expanding hematomas, and oozing from the vascular access site. Separately, although one ex vivo experiment showed that PCCs restored thrombin generation in plasma previously taken from patients receiving dabigatran, a small randomized

trial showed that PCCs had no effect on coagulation parameters in such patients in vivo.[4,5] Importantly, these individuals had normal liver and kidney function. A trial of PCCs in patients with ESLD with coagulopathy has been proposed, but until more robust clinical data are available, PCCs should be used cautiously to manage hemorrhage in patients with ESLD and AKI.[6]

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