COMMENT

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Rivaroxaban-related nephropathy

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In the last issue, Oliveira et al presented a case of an 82-year-old woman under rivaroxaban treatment with previous normal renal function, admitted with gross hematuria and acute kidney injury. A renal biopsy revealed typical features of anticoagulant-related nephropathy (ARN) superimposed on chronic interstitial nephritis.[1]

To the best of our knowledge, this is the first report that describes ARN associated to rivaroxaban. This follows the idea that ARN, firstly related to warfarin,[2] represents a broader syndrome that includes novel oral anticoagulants (NOACs).

NOACs are alternatives to Vitamin K antagonists (VKA) in cardiovascular disease such as atrial fibrillation and venous thromboembolism. They include a thrombin inhibitor (dabigatran), and three factor Xa inhibitors (rivaroxaban, edoxaban and apixaban).[3] A predictable pharmacokinetic profile and unnecessary routine coagulation evaluation make their prescription very appealing.[3] Still, questions remain about their safety with respect to renal function and kidney outcomes, as well as hemorrhagic complications.

ARN has been recognized as a significant complication of anticoagulation, associated with increased renal morbidity and all-cause mortality. Its incidence in a cohort of patients starting warfarin was estimated to be 20.5% of the entire cohort, 33.0% of the CKD cohort, and 16.5% of the no-CKD cohort.[4]

ARN related to dabigatran has been reported. Further, in the animal model, the risk to ARN was found to be dose-dependent and higher to dabigatran than to warfarin, especially in a population with normal kidney function.[5]

Apixaban, dabigatran and rivaroxaban, showed a similar risk of renal failure compared with other anticoagulants in phase III RCTs. Even so, rivaroxaban showed an increased risk of creatinine elevation.[6] An ongoing trial in the Albert Einstein Healthcare Network, USA, designed to find the incidence of ARN in patients who are started on rivaroxaban, may shed light on this question.

ARN may be easily overlooked since its main risk factors, chronic kidney disease (CKD) age, diabetes mellitus, heart failure and hypertension, are common for acute kidney injury (AKI) from any cause.[4] In such patients, an extensive diagnostic evaluation in the setting of AKI is usually not performed. In addition, a kidney biopsy may be delayed or avoided in the setting of anticoagulation.

Diagnosis of ARN, then, is mainly clinical. ARN is defined as an episode of AKI without obvious etiology in the setting of an International Normalized Ratio (INR) of > 3.0.[7] While with VKAs a high INR would sound the alarm of ARN, when it comes to NOACs, we no longer have that support, which make its diagnosis more challenging and the present definition of ARN outdated.

As if that wasn't enough, ARN is characterized by glomerular hemorrhage, dysmorphic red blood cells (RBCs) obstructive tubular RBC casts, ischemia, and eventual obliteration, associated with interstitial hemorrhage, that leads to increased oxidative stress in the kidney and CKD.[2]

This pattern is common to several diseases responsible for hematuria such as IgA, LES, GESF, anti-GBM.[2] In fact these entities can be coincidental with glomerular disease representing perhaps a first hit, increasing the risk of these individuals of developing ARN. Pinpointing the true role of each factor in the setting of hematuria can be challenging. Overcoagulation, and the absence of proteinuria or histological markers of

glomerular disease as endocapillary hypercellularity, active glomerulonephritis or other inflammatory changes that could account for glomerular hemorrhage make ARN more likely.[2,8,9] If preexisting glomerular disease constitutes a risk factor or a predisposing condition remains still to be elucidated.

Also, a similar underlying molecular mechanism may be common to these diseases. Glomerular hydrostatic pressure, thrombin depletion and activation of proteinase-activated receptors (PARs) and protein C may be responsible for glomerular fragility and endothelial disfunction and have been hypothesized as possible causes of ARN.[7]

Treatment of ARN is mainly supportive and includes decreasing the anticoagulation to prevent continued glomerular hemorrhage and additional kidney tubular damage. Without specific treatment to offer, early detection and prevention in really the gold standard.

The precise classification of CKD is essential, especially in the elderly, since it will define the type and dose of the NOAC prescribed.

All NOACs have renal excretion: dabigatran > 80%; rivaroxaban 66%; edoxaban 33% and less extensively apixaban 25%. As renal impairment potentiates the bleeding risk so the dose must be adjusted.[3]

Apixaban can be used in advanced chronic kidney disease (CKD) and even in end-stage renal disease, but the use of dabigatran, rivaroxaban and edoxaban is not recommended in patients with advanced CKD.[3] Even so, rivaroxaban, for example, presents a wide therapeutic range with an identical dose for patients with GFR between 15–50 mL/min, meaning that patients may be exposed to supratherapeutic doses and toxicities. Also, classifying CKD in the elderly may be difficult due to the physiological decrease of GFR, nutritional status and loss of muscular mass.

Also, we must not forget other factors that may interfere with the metabolism of NOAC, such as liver disfunction, and concomitant medication that alter drug concentration (interference with CYP3A4 or P-glycoprotein) or increase the bleeding risk (acetylsalicylic acid, clopidogrel, ibuprofen, diclofenac).[3]

Finally, prompt recognition of ARN is critical. ARN should be considered in the differential diagnosis of any patient receiving anticoagulation and presenting with AKI. The presence of hematuria (gross or microscopic) in the absence of a clear etiology for the AKI makes the diagnosis of ARN highly likely. However, its absence does not exclude this diagnosis.

Renal function needs closer monitoring in patients (especially elderly ones or those with advanced CKD) taking NOACs. Also, monitoring of coagulation by determination of activity of target coagulation factors or the measurement of circulating drugs may become a useful tool in minimizing side effects. Taken together, this may partly outweigh the benefits of not monitoring coagulation parameters with NOACs.[7]

In sum, NOACs may be responsible for new episodes of AKI and development of CKD even in a population with a previous normal kidney function. This can become an important clinical problem as NOACs prescription is increasing.

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