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Review Article

Anticoagulants and acute kidney injury: clinical and pathology considerations

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Abstract

We have recently identified a new clinical syndrome in patients receiving warfarin for anticoagulation therapy. This syndrome has been named warfarin-related nephropathy (WRN), and patients with chronic kidney disease (CKD) appear to be particularly susceptible. WRN is defined as an acute increase in international normalized ratio (INR) to >3.0, followed by evidence of acute kidney injury (AKI) within 1 week of the INR increase. AKI was defined as a sustained increase in serum creatinine of greater than or equal to 0.3 mg/dL. The AKI cannot be explained by any other factors, and the kidney biopsy demonstrates extensive glomerular hemorrhage with tubular obstruction by red blood cells (RBCs). Beyond AKI, WRN is a significant risk factor for mortality within the first 2 months of diagnosis and it accelerates the progression of CKD. We demonstrated that 5/6 nephrectomy in rats is a suitable experimental model to study WRN. Animals treated with warfarin showed an increase in serum creatinine and morphologic findings in the kidney similar to those in humans with WRN. Our recent evidence suggests that novel oral anticoagulants may induce AKI. Diagnosis of WRN may be challenging for a renal pathologist. A few cases with suspected WRN and pathologic considerations are described.

Introduction

Anticoagulant therapy is vital for patients with thromboembolic disorders, most notably atrial fibrillation or deep vein thrombosis. An estimated 4 million patients in the US and almost 7 million worldwide are receiving long-term therapy with oral anticoagulants, primarily warfarin or other coumarin derivatives, for prevention and treatment of venous and arterial thromboembolism [1]. Vitamin K antagonists, such as warfarin (Coumadin), provide reliable protection against thromboembolic events. However, this benefit comes at a cost, which is a risk of hemorrhage resulting from coagulopathy. Recently, evidence that warfarin-related coagulopathy may lead to kidney complications, including acute kidney injury (AKI), was reported [2–4]. This complication was reported in the USA [2–4] and Korea [5]. Worrisome data that even novel oral anticoagulants may also affect the kidney were recently reported [6,7].

This review focuses on the discovery of anticoagulant-related kidney injury, describes an animal model to study it, and provides guidance for nephrologists and renal pathologists who may encounter this disease.

Clinical aspects of anticoagulation and AKI

Chronic kidney disease (CKD) is one of the major health problems in the world [8], where between 10% and 15% of the population are diagnosed with this condition [9,10]. Anticoagulation therapy is commonly required in CKD patients for treatment

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or prevention of thromboembolic disorders. It has been shown that CKD patients are at high risk of developing atrial fibrillation, which requires anticoagulation therapy, and as many as 21% of nondialysis CKD patients may have atrial fibrillation, as compared with 1.5–6.2% in the general population [11]. Among the patients diagnosed with atrial fibrillation, more than a third have CKD Stage 3 and above [12]. Warfarin is the most prescribed anticoagulant in the world and more than 2 million people start warfarin therapy every year in the USA alone. Warfarin treatment requires constant monitoring of the international normalized ratio (INR) and dose adjustments should be made to keep the INR within the therapeutic range. Monitoring of INR is difficult, costly, and there is a level of noncompliance. CKD is associated with decreased anticoagulation stability in patients on warfarin therapy, which, in turn, requires more frequent and intensive clinical management [13]. Avoiding over-anticoagulation in CKD appears to be a frequent problem. Limdi et al [14] compared complications of warfarin therapy among 578 patients with different stages of CKD. They reported that patients with severe CKD were at higher risk for both over-anticoagulation and major hemorrhage, as compared with patients with mild or moderate CKD. Chan et al [15] reported that warfarin therapy is associated with higher mortality among hemodialysis patients than in non–end-stage renal disease (ESRD) CKD patients. Their study included 41,425 hemodialysis patients; 8.3% were receiving warfarin therapy. Warfarin therapy was associated with a 27% increase in mortality.

Several adverse effects of warfarin overdose on kidney function have been described, including hemorrhages, vasculitis, interstitial nephritis, and hematuria [16,17]. Our group described AKI associated with warfarin treatment [2–4]. We named this condition warfarin-related nephropathy (WRN).

It has been suggested that warfarin can cause AKI by inducing glomerular hematuria with subsequent widespread tubular obstruction. This was first reported in a patient with severe warfarin coagulopathy and thin glomerular basement membrane (GBM) disease [18]. Later, evidence of a similar syndrome in a patient with inactive systemic lupus erythematosus (SLE), with an abnormally thick GBM, was reported [19].

The mechanism of the AKI in these patients likely involved the unusual combination of very severe warfarin coagulopathy (INR in the 6–9 range) in which the patient had either abnormally thin GBM [18] or abnormally thick GBM [19], both of which are risk factors for spontaneous gross hematuria [20]. Thus, based on these cases, there was no compelling reason to believe that AKI would be a common complication of warfarin therapy. This notion, however, was dispelled by our kidney biopsy study of nine instances of WRN in seven patients who developed unexplained AKI during only moderate over-anticoagulation with warfarin (mean INR 4.4 ± 0.7) [4]. The kidney biopsies showed widespread and severe tubular obstruction by red blood cell (RBC) casts. Although these patients had CKD, their glomeruli were normal or showed only minor changes. Thus, the renal biopsy evidence of severe glomerular hematuria was unexpected. Also, most of the WRN patients showed little or no recovery of kidney function [4].

The next work by our group was a retrospective analysis of 103 consecutive warfarin-treated CKD patients followed in our Nephrology program from January 2005 until June 2009. Of these, 49 experienced at least one episode of INR > 3.0. Of these, 18 (37%) developed an unexplained increase in serum creatinine $\geq$ 0.3 mg/dL within 1 week of the INR > 3.0, and their CKD progression was accelerated [2].

Another evidence of the broad clinical significance of WRN is an analysis of 4,006 warfarin-treated patients [3]. Each experienced an INR > 3.0 and serum creatinine was measured within 1 week of the increased INR. The analysis of this large database (4,006 patients) [3] supports the analysis of the smaller database (103 patients) [2] that showed that WRN is common in CKD patients (37% develop AKI at first onset of INR > 3.0). The new insight of this study is that WRN is also common in no-CKD patients and is significantly associated with an increased risk of mortality.

Based on these publications, the key clinical features of WRN are: (1) evidence of AKI appears shortly after the INR acutely increases to > 3.0; (2) kidney biopsies in these patients show acute tubular injury associated with severe and widespread occlusive RBC casts; (3) WRN accelerates the progression of CKD; (4) WRN occurs in approximately 37% (CKD) to 16% (no-CKD) of warfarin-treated patients whose INR acutely rises to > 3.0; (5) patients with WRN have a significantly increased mortality rate.

We observed that WRN may occur in some patients who do not have the clinical diagnosis of CKD. Our experimental data show that control animals treated with warfarin do not develop AKI even if their prothrombin time (PT) increases more than five times [21,22]. This raises the possibility that the people who develop WRN without apparent CKD probably had some underlying kidney injury.

Several other groups have described WRN in patients on warfarin therapy [5,23]. Their data confirmed our observations, including a high incidence of WRN. The main conclusions from published data are:

- The risk of AKI occurs at an INR threshold of > 3; AKI risk is not a function of the level of INR beyond 3.
- The kidney biopsy findings in those with AKI and INR > 3 are consistent with catastrophic glomerular hemorrhage causing tubular injury.
- An abnormally elevated INR is not sufficient by itself to cause WRN; we postulate that WRN occurs in the setting of pre-existing glomerular damage (which may not have been clinically known/diagnosed) coupled with over-anticoagulation. Normal patients who develop WRN likely have undiagnosed CKD/glomerular injury.
- When specifically analyzed, WRN is associated with progression of CKD and an increased risk of subacute mortality.
- The true incidence of WRN is difficult to determine from the mainly retrospective studies published thus far, but it appears to be high. The only prospective study [23] suggests an incidence of 60%, at least in the elderly population examined.

Adding to this public health problem is emerging evidence that WRN is only a subset of a broader syndrome, that probably is anticoagulant-related nephropathy (ARN) in which other, and possibly all, currently used anticoagulants may cause AKI. Indeed, AKI associated with dabigatran (direct thrombin inhibitor) use has been reported in humans [6,24,25] and was recently demonstrated by our group in experimental animals [7]. In addition, anticoagulants may aggravate an underlying kidney disease and induce hematuria and AKI [26].

Experimental models of WRN

First, our group demonstrated that excessive anticoagulation by superwarfarin (brodifacoum) reproduces morphologic