Anticoagulation and kidney injury: rare observation or common problem?

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Vitamin K antagonists (VKAs), which inhibit the synthesis of the coagulation factors II, VII, IX and X, have been in clinical use since the 1950s to treat thrombotic disease. Recently, new indications for long-term anticoagulation have been recognised. Consequently the number of patients prescribed long-term anticoagulant therapy with VKAs is increasing. Warfarin is the most commonly prescribed VKA, but acenocoumarol and phenprocoumon are also widely used in Europe. Patients with chronic kidney disease (CKD) are at a relatively higher risk of thromboembolic disease. In addition, patients on long-term warfarin often have multiple comorbidities placing them at risk of kidney disease. Therefore, warfarin is a commonly used drug in CKD patients. There are obvious dangers of overanticoagulation, most importantly the risk of haemorrhage, a complication which is twofold more common in patients with CKD (1). Maintaining warfarin within its narrow therapeutic range can be more difficult in patients with CKD, and overt, hypovolaemic blood loss resulting from overanticoagulation can precipitate acute kidney injury (AKI). However, warfarin use alone was not traditionally thought of as a cause of kidney injury.

This view has changed recently with a number of reports of warfarin causing AKI, a phenomenon now referred to as warfarin-related nephropathy. Warfarin was first proposed as a cause of AKI in a patient with thin basement membrane disease who developed macroscopic haematuria and AKI on initiation of warfarin therapy (2). This patient had a disease predisposing to haematuria, and since that account there have been other case reports of warfarin-related macroscopic haematuria and AKI in patients harbouring preexisting glomerular disease (3, 4). In a case series of 9 individuals presenting with unexplained haematuria and AKI whilst on warfarin (3), an underlying renal disease was evident in all 9 biopsies. The outcome after warfarin-related nephropathy was poor in this series; 4 patients remained dialysis-dependent, and a further patient was dialysis-independent but did not recover renal function.

In this issue of the Journal of Nephrology, van Blijderveen et al report an association between overanticoagulation and progression of CKD (5). This is potentially an important association, given the high rate of warfarin use in the CKD population and the need to minimise the risk of kidney injury in these patients. The report uses data from the Rotterdam study, a prospective population-based cohort study involving over 10,000 people aged 55 years or older living in the Rotterdam area. In this group, serum creatinine was measured in 2,802 patients at the start of the study and again a median of 6.5 years later. During this period, 354 participants were treated with VKAs, so although the investigators started with a large cohort, the number of patients included in the study was rather smaller. In addition, treatment time was short, with a median VKA exposure of 251 days, representing only a proportion of the observation period. During treatment, 181 episodes were identified in which the international normalized ratio (INR) was greater than 6. The key finding in this study was that each documented episode (INR >6) was associated with a more rapid decline in estimated glomerular filtration rate (eGFR) over the study period, an excess of 0.18 ml/min per 1.73 m² per year compared with the cohort as a whole. This effect was cumulative, with the rate of loss increasing by this amount with each documented INR above 6. Creatinine measurements were not available for the start and end of VKA treatment. Knowing that the accelerated loss of eGFR occurred whilst the patient was on a VKA would have made a rather stronger case for VKA treatment being the actual cause of eGFR decline. The absence of these measurements is a weakness of the study. Importantly, accelerated eGFR loss was not associated with VKA use in the absence of overanticoagulation. These data therefore suggest that neither therapeutic VKA use nor the indication for anticoagulation – for example, cardiac disease – is responsible for the more rapid loss of eGFR.

This study is consistent with the hypothesis that glomerular bleeding occurs at times of overanticoagulation, resulting in
subclinical episodes of AKI and a more rapid decline in renal function. If correct, the more rapid loss of GFR seen in patients with high INRs will occur over the short period of overanticoagulation. Reporting the rate of eGFR loss over the whole study period will underestimate the rate of loss during the period of overanticoagulation. The current report suggests that anticoagulation only damages the kidney if the INR is significantly outside the therapeutic range (INR >6). The number of anticoagulated participants in this study was small, meaning that it may have been insufficiently powered to detect an effect at lower INRs. Brodsky et al in 2011 studied over 15,000 patients who initiated warfarin therapy (6). A rise in creatinine (>0.3 mg/dL) within 1 week of an INR >3 was observed in 20% of the patients. Almost identical rates of AKI have also recently been described in an Asian population at the same INR level (7). Therefore damage may be occurring even at INR levels within, albeit at the high end of, the therapeutic range. In addition, an INR of 3 or more may be sufficient not only to cause an acute decline in renal function, but to accelerate the rate of progression of CKD (8).

The majority of participants in the Rotterdam study had well-preserved renal function at recruitment, suggesting that warfarin can cause renal injury irrespective of the presence of preexisting renal disease. This is consistent with the observation that, although acute warfarin-related nephropathy is more common in patients with CKD and an INR >3 (33%), it also occurs in patients without CKD (16%) (6). In addition to CKD, risk factors for acute warfarin-related nephropathy include age, diabetes mellitus, hypertension and cardiovascular disease.

These clinical observations provoke stimulating biological questions regarding the biochemical mechanism(s) of warfarin-related nephropathy. Because the study by van Blijderveen et al (5) was a retrospective analysis, no data are available to help answer such questions; in particular, no examination of the urinary sediment and no biopsy analyses are available. The presence of red blood cells in Bowman’s space in patients who underwent biopsy in previous studies indicates glomerular bleeding is occurring and suggests that an intact coagulation cascade is needed to maintain integrity of the glomerular filtration barrier. Many glomerular diseases cause microscopic haematuria. When the coagulation cascade is inhibited, particularly if this exceeds therapeutic boundaries, additional bleeding can occur from the glomerulus into Bowman’s space causing AKI. It is perhaps easier to understand why anticoagulation will increase bleeding from a diseased glomerulus. Why an intact coagulation cascade is needed to maintain capillary integrity within a normal glomerulus is less clear. The clinical studies show that warfarin-related nephropathy can occur in the absence of renal disease (6), implying that glomerular bleeding occurs even from the normal glomerulus if coagulation is inhibited. The mechanism for this is not known.

A second question is how glomerular haematuria leads to AKI. Brodsky et al (3) suggest that this is due to tubular obstruction by red cell casts, based on the histological appearance of renal biopsies from their case series of warfarin-related nephropathy. Macroscopic haematuria is known to be associated with a transient decline in renal function in patients with IgA nephropathy, and tubular obstruction has also been proposed as a cause for reduced GFR in these patients. However, studies have failed to show evidence of reverse flow of tubular proteins, which might be expected in obstructed tubules (9). Additionally, macroscopic haematuria is not a feature of the cases of warfarin-related nephropathy identified in the population-based studies, questioning whether tubular obstruction is the cause of AKI in all cases. An alternative explanation is that substances such as iron, released from tubular red cells, are toxic to tubular epithelial cells (10). This is consistent with the case series studied by Brodsky et al (3), in which evidence of acute tubular cell injury was observed in addition to occlusive casts. Warfarin use can induce other forms of AKI – for example, interstitial nephritis (11) – and renal biopsy should be considered, no matter how challenging, in patients on warfarin with unexplained AKI.

The body of evidence that anticoagulation with VKAs can cause kidney injury is increasing. It certainly can cause AKI, and studies similar to that presented by van Blijderveen et al suggest anticoagulation can also accelerate the progression of CKD, perhaps due to multiple subclinical episodes of AKI. Current evidence would suggest that the higher the INR, the more likely this is to occur. Larger prospective studies are still required in this area to identify at-risk patients and the INR level that predisposes to AKI. Additionally, we anticipate novel studies examining whether or not second-generation, non-VKA anticoagulants could mimic the effects of warfarin on renal function. Such studies could impart some of the currently lacking mechanistic knowledge. In the meantime, a degree of caution is required when using anticoagulants in patients with CKD.

Financial support: None.

Conflict of interest: None.

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Accepted: April 30, 2013