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Haematuria and Acute Kidney Injury Associated with Warfarin Anticoagulation

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Abstract

Bleeding is a common complication of warfarin anticoagulation and not uncommonly affects the kidney and urinary tract. This review explores the potential causes of haematuria and acute kidney injury in patients receiving warfarin treatment. It covers urological aspects as well as the recently described warfarin-related nephropathy and other less common causes of kidney injury related to warfarin treatment.

Keywords: Warfarin; Warfarin-related nephropathy; Haematuria; Acute kidney injury; Chronic kidney disease

Background

The use of warfarin to treat glomerulonephritis and various renal diseases was practiced in many countries in the 1970s and early 1980s [1-5]. However, the pendulum may have swung the other way in recent years, with concern that warfarin may be detrimental to the kidneys in the long term. There is interest in the development of acute kidney injury (AKI) associated with warfarin therapy and possible poor outcomes in susceptible groups.

Warfarin is an oral anticoagulant which inhibits vitamin K dependent γ-carboxylation of clotting factors II, VII, IX and X. The main indications for warfarin are treating and preventing thrombo-embolism. Although effective, warfarin use is potentially complicated by supratherapeutic anticoagulation (overanticoagulation). Warfarin is strongly protein bound, mainly to albumin. Albumin is a negative acute phase reactant and many illnesses reduce serum albumin. Warfarin is mainly metabolised by the CYP-2CP microsomal liver enzymes, which may be affected by a number of medications. Thus, medication interactions and medical conditions may predispose patients to supratherapeutic anticoagulation. The prothrombin time, standardised as the International normalized ratio (INR) is used to monitor warfarin anticoagulation. Warfarin reversal may be achieved by administering vitamin K.

Haemorrhage is the main complication of concern with warfarin therapy. The top three sites of bleeding are the oropharynx, soft tissue, gastrointestinal and urinary tract [6]. In one study, the average annual frequency of major bleeding was 3%, with 15% of major bleeding originating from the urinary tract. However, there is a wide variation is bleeding figures, depending on the INR target, patient characteristics and definitions used. Patients with chronic kidney disease (CKD) have an increased risk of overanticoagulation as they spent less time in the therapeutic range, required frequent dose adjustments and had higher bleeding risk [7,8].

Briefly, AKI is typically considered by mechanism as prerenal, intrinsic (intrarenal), and postrenal (obstructive); all of which may be involved in warfarin-treated patients. This review explores the possible causes of haematuria and AKI which may be attributed to a complication of anticoagulation with warfarin.

Urological Considerations

Urinary tract bleeding in the setting of warfarin anticoagulation commonly presents as haematuria. Bleeding from the kidney may be retroperitoneal, intraluminal or intrarenal [9]. Intrarenal bleeding may be suburothelial, intraparenchymal, subcapsular, perinephric or pararenal [10,11]. Intrarenal and intraluminal bleeding uncommonly leads to obstructive uropathy and postrenal AKI. Shock from massive retroperitoneal bleeding or kidney rupture may lead to prerenal AKI but are also uncommon.

Haematuria and suburothelial bleeding

Decades ago, the source of haematuria in anticoagulated patients was a mystery. Dajani, in a letter to the New England Journal of Medicine in 1977 wrote "I have looked in vain for a description of the mechanism of hematuria in patients on anticoagulants [12]". He subsequently described a patient who presented with macroscopic haematuria following warfarin overanticoagulation. The patient had a nephrectomy due to the concern of a malignant cyst on the pyelogram. Microscopic examination of the kidney showed multiple foci of haemorrhage in the pelvicalyceal wall, ranging from subepithelial haemorrhage to rupture of the epithelium and frank leaks into the urinary channels. In addition to this histopathological description, numerous radiological reports have demonstrated bleeding within the pelvicalyceal system related to anticoagulation [9,13-18]. The suburothelial haematoma in the renal pelvis may mimic a tumour, the so-called Antopol-Goldman lesion [19,20]. The majority of such patients with pelvicalyceal bleeding present with macroscopic haematuria and flank or back pain. These patients have often ended up with unnecessary nephrectomies as radiological studies were unable to exclude transitional cell carcinoma.

In a recent study by Gayer et al. [21], seven patients with coagulopathy and spontaneous suburothelial haemorrhage diagnosed by CT were analysed. Six patients had abdominal or flank pain, and 5/6 had macroscopic haematuria. One patient had painless haematuria. Five of the patients had supratherapeutic warfarin anticoagulation (INR 5-12, average 8.1), while one was at the upper limit of the therapeutic range and the other thrombocytopenic. All seven patients demonstrated high-density mural thickening in the renal pelvis on unenhanced CT, which extended into the proximal ureters in 5 patients.

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