Case Report

Renal tubular injury associated with anagrelide use

Graham E. J. Rodwell1, Megan L. Troxell2 and Richard A. Lafayette1

1Division of Nephrology and 2Department of Pathology, Stanford University School of Medicine, Stanford, CA, USA

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Introduction

We describe the first case of biopsy-proven renal tubular injury associated with anagrelide.

Case

A 60-year-old man with a 35 year history of Crohn's disease was diagnosed with essential thrombocytosis (ET) following a unilateral renal artery thrombosis in May 2003. His platelet count at the time of diagnosis with ET was 1.3 million cells/mm3.

He began taking 0.5 mg oral anagrelide twice daily, increasing the dose to 1 mg each morning and 0.5 mg each evening over the next weeks and, finally, to 1 mg twice daily. His concurrent medications were azathioprine, mesalamine, sulphasalazine, B12 injections, multivitamins, aspirin and iron polysaccharide. He took no over-the-counter medications. He demonstrated an excellent response to anagrelide, with a reduction in platelet count to 300,000 cells/mm3 after 1 month of therapy.

Previous to starting anagrelide, he had stable renal function with a serum creatinine concentration consistently between 1.4 and 1.8 mg/dl. His creatinine concentration rose to 2 mg/dl after 1 month of treatment, to 2.5 mg/dl after 4 months, 2.8 mg/dl after 6 months and 3.4 mg/dl after 10 months (Figure 1). His serum potassium concentration rose from a baseline of <4 mEq/l to a high of 6.1 mEq/l at the peak of renal dysfunction. Urinalysis showed low-grade proteinuria (300–500 mg/day) without formed elements or cells.

Renal ultrasound and magnetic resonance imaging after 6 months of treatment demonstrated a normal kidney on one side, with the formerly infarcted kidney shrunken on the other side. A renal biopsy after 10 months of treatment demonstrated features of acute tubular injury. The biopsy included renal cortical and medullary tissue; the nine sampled glomeruli were unremarkable, with the exception of one globally sclerotic glomerulus. Scattered tubules, most notably proximal tubules, were ectatic with shortening and rounding of epithelial cells, large nuclei with prominent nucleoli and, in rare tubules, loss of epithelial cells (Figure 2). A rare tubular mitotic figure was observed. Some tubular epithelial cells also contained minute periodic acid–Schiff (PAS)-positive vesicles. Acellular hyaline casts were present within medullary tubules. There was <5% tubular atrophy and minimal infiltration of lymphocytes, without eosinophils. Trichrome and Congo red staining demonstrated no increase in interstitial fibrosis or amyloid deposition, respectively. Intralobular arteries demonstrated mild arteriosclerosis, with focal hyalinosis; arterioles were unremarkable.

Following the biopsy, anagrelide was discontinued and hydroxyurea was started at 500 mg daily. There were no other changes to his medication regimen. His serum creatinine concentration subsequently fell to 3.0 mg/dl after 1 week, to 2.8 mg/dl after 5 weeks, to 2.5 mg/dl after 3 months and to 2.15 mg/dl after 9 months.

Discussion

Anagrelide is a derivative of quinazoline, whose main action is to inhibit the differentiation of megakaryocytes [1]. It was first used in clinical trials in 1992 [2]. Along with hydroxyurea, it is widely considered to be a first-line treatment for thrombocytosis. It is commonly used as an alternative to hydroxyurea, which carries a risk of leukaemogenesis. Few studies have examined its potential toxicity. The known side
Fig. 1. Serum creatinine and platelet count. Serum creatinine concentration (open circles) and platelet count (closed circles) are plotted as a function of time. Start and end dates of anagrelide therapy are marked.

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Fig. 2. Histopathological features on renal biopsy. (A) Ectatic cortical tubules with attenuated epithelial cells and loss of brush border (arrows). PAS stain; magnification: ×600. (B) Ectatic tubules (arrow) and large nuclei with prominent nucleoli (arrowheads). Protein casts and scattered lymphocytes are also present in sections from the outer medulla. Haematoxylin and eosin stain; magnification: ×400.
effects include decreases in vascular tone as well as arrhythmias, heart failure and headaches [3].

Renal failure as a complication of anagrelide therapy is not well recognized. One long-term prospective study evaluating the toxicity of anagrelide treatment has been performed. Of the 120 patients included in the study, one developed acute interstitial nephritis. No other cases of nephrotoxicity were reported [4]. In an initial study of 942 patients receiving anagrelide, six patients experienced renal failure while taking the drug. Of these, four were considered to be possibly related to the anagrelide. The specific pathology was not reported [5]. No previous cases of acute tubular injury have been described and no other studies that we are aware of have reported nephrotoxicity. Remarkably, in the present, case the recovery has been ongoing, but quite slow.

This case strongly suggests a role for anagrelide in causing tubular necrosis. The precise mechanisms of such injury are not known. As this drug becomes more widely used, physicians should be aware of this potential complication.

Conflict of interest statement. None declared.

References


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