Case in Point

Urolithiasis in a Patient With HIV Receiving Atazanavir

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A 61-year-old man with HIV who had a history of renal stone development presented with bilateral renal stones within 5 months of switching from an efavirenz- to an atazanavir-based therapy. The patient's high creatinine levels dropped after undergoing a bilateral lithotripsy along with stenting of his right ureter due to obstructive uropathy. Infrared analysis of the stone showed the composition to be 97% atazanavir.

Atazanavir is a protease inhibitor (PI) indicated for the treatment of human immunodeficiency virus (HIV) as part of the highly active antiretroviral therapy (HAART). Limited data exist documenting the risk of patients developing urolithiasis while being treated with certain antiretroviral therapies. However, the risk of urolithiasis due to administration of atazanavir seems to exceed the combined risk associated with other drugs used for treatment of HIV. Development of a right-sided urethral calculus related to atazanavir therapy in a patient with HIV is described in this case study.

CASE STUDY

A 61-year-old man diagnosed with HIV in 1991 presented to Bay Pines Veterans Affairs Healthcare System in Florida in November 2008 to establish his medical care. He had been on efavirenz-based therapy. His past medical history included 3 incidents of renal stone development between 1970 and 1990, which were successfully passed without medical intervention. On initial evaluation, the patient's laboratory data revealed an undetectable HIV viral load, a CD4 count in the range of 200 cells/μL, and creatinine (Cr) and bilirubin levels at 0.97 mg/dL and 0.4 mg/dL, respectively.

In September 2010, the option of considering a PI-based HARRT regimen was discussed with the patient due to previous data supporting that patients infected with HIV treated with PIs may have improvements in their CD4 T-cell numbers.[1] The patient shared his concern about his chronic low CD4 count; thus, the patient's antiviral treatment was changed to emtricitabine/tenofovir disoproxil fumarate, atazanavir, and ritonavir. In February 2011, the patient's Cr rose to 1.38 mg/dL, and in July, it rose again to 1.42 mg/d. The tenofovir dose was adjusted accordingly. In early August 2011, the patient's Cr was elevated at 2.08 mg/dL. At that time, the patient was admitted to a community hospital due to complaints of worsening right flank pain for the duration of 3 days.

The patient was found to have bilateral renal stones. He underwent a bilateral lithotripsy along with stenting of his right ureter due to obstructive uropathy. Shortly following the urology procedure, the patient's Cr dropped to 1.30 mg/dL. Infrared laboratory analysis of the stone showed the composition to be 97% atazanavir. The patient's atazanavir and ritonavir were discontinued. Nelfinavir was started as a new PI and emtricitabine/tenofovir disoproxil fumarate was continued at the standard dose. Since the medications were changed, the patient did well without further renal issues.

DISCUSSION

A limited number of cases have been reported indicating patients with HIV who are treated with PIs may be at an increased risk for renal stones. In the literature, an increased risk of renal stones in patients treated with atazanavir has been reported compared with other HIV drug regi-

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mens.[2] However, kidney stones have also been documented in patients receiving various other PIs, such as indinavir and lopinavir.[2] Atazanavir is approved for administration as a once-daily dose of 300 mg boosted with 100 mg of ritonavir. Atazanavir is similar to indinavir, as both are primarily metabolized and eliminated by the liver through multiple pathways, including the CYP3A4 pathway, which forms 2 inactive metabolites. Both indinavir and atazanavir are slightly soluble in water (4-5 mg/mL) with a pH-dependent solubility.[2] Despite liver metabolism, 13% of a 400-mg dose of atazanavir is recoverable in the urine, of which 7% is unchanged; 79% is excreted in the feces, which represents 20% of the drug being unchanged.[3]

Common clinical adverse effects (AEs) associated with atazanavir include asymptomatic elevations in unconjugated bilirubin; fat redistribution (due to increased glucose and lipids; however, these AEs are less frequent in atazanavir compared with other PIs); and hypersensitivity reactions, including rash, angioedema, anaphylaxis, and bronchospasm. Other noted AEs may include immune reconstitution syndrome and nephrolithiasis (which has been reported in postmarketing surveillance).[3] A meta-analysis from 2004 to 2007 documented that of 1,134 patients treated with atazanavir, 11 patients received a diagnosis of atazanavir-associated urolithiasis with an overall prevalence of 0.97%.[2] Chan-Tack and colleagues identified 30 cases of nephrolithiasis in patients infected with HIV taking an atazanavir-based regimen from December 2002 to January 2007.[4]

The mechanism for PI-associated nephrolithiasis remains unknown. Rockwood and colleagues found several patients had comorbidities, such as hepatitis C, hepatitis B, preexisting renal disease, or a history of nephrolithiasis.[5] In addition, a high urinary pH was a factor that may have increased the likelihood of urinary crystallization.[5] The maximal solubility of atazanavir takes place at a pH of 1.9.[2] Thus, a high urinary pH tends to favor atazanavir precipitation. Couzigou and colleagus reviewed stone analysis of 11 patients diagnosed with atazanavir-associated urolithiasis. The stones contained atazanavir crystals; 8 stones had an atazanavir core and 4 had a calcium oxalate core (1 patient had 2 stones).[2]

Studies have shown that patients taking atazanavir who developed nephrolithiasis contained a stone composition in the range of 40% to 100% of atazanavir concentrations.[4] Rockwood compared the incidence of stones in a cohort of 6,255 patients undergoing antiretroviral regimens containing atazanavir, efavirenz, lopinavir, and darunavir.[5] Of the 1,206 patients who received atazanavir, 24 (2%) developed renal stones.[5] In 2006, Chang and Pella reported a patient who developed atazanavir-related urolithiasis. However, the patient had a history of mild renal insufficiency. His Cr level was 1.6mg/dL when the diagnosis of urolithiasis was made.[6] The patient underwent a cystoscopy with right ureteroscopic extraction and stent placement. On stone analysis, the composition was determined to be 60% atazanavir and 40% calcium phosphate.[6]

CONCLUSION

Clinicians should be aware that patients receiving atazanavir therapy, especially patients with a history of urolithiasis or renal disease, may be at risk for urinary crystal formation compromising their renal function. Considerations for alternative regimens should be explored. ●

Author disclosures

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REFERENCES

1. Kravcik S, Magill A, Sanghvi, et al. Comparative CD4 T-cell responses of reverse transcriptase inhibitor therapy with or without nelfinavir matched for viral exposure. *HIV Clin Trials.* 2001;2(2):160-170.
2. Couzigou C, Daudon M, Meynard JL, et al. Urolithiasis in HIV-positive patients treated with atazanavir. *Clin Infect Dis.* 2007;45(8):e105-e108.
3. Atazanavir: Drug information. *UpToDate*. Waltham, MA: UpToDate; 2013. http://www.uptodate.com/contents/atazanavir-drug-information?topickey=DRUG_GEN%2F9353. Accessed October 15, 2013.
4. Chan-Tack KM, Truffa MM, Struble KA, Birnkrant DB. Atazanavir-associated nephrolithiasis: Cases from the U.S. Food and Drug Administration's adverse event reporting system. *AIDS.* 2007;21(9):1215-1218.
5. Rockwood N, Mandalia S, Bower M, Gazzard B, Nelson M. Ritonavir-boosted atazanavir exposure is associated with an increased rate of renal stones compared with efavirenz, ritonavir-boosted lopinavir and ritonavir-boosted darunavir. *AIDS.* 2011;25(13):1671-1673.
6. Chang HR, Pella PM. Atazanavir urolithiasis. *N Engl J Med.* 2006;355(20):2158-2159.