Abacavir-induced reversible Fanconi syndrome with nephrogenic diabetes insipidus in a patient with acquired immunodeficiency syndrome

Ahmad M

ABSTRACT
There are several reports of Fanconi syndrome (FS) with or without nephrogenic diabetes insipidus (NDI) in patients with human immunodeficiency virus (HIV) infection, treated with various antiretroviral medications like cidofovir,[1] adefovir,[2] didenosine[3] and tenofovir[4] therapy are well-described. Our search of the literature did not reveal any case of FS with or without NDI associated with abacavir therapy in patients with acquired immunodeficiency syndrome (AIDS). We are reporting the first case of abacavir-induced reversible FS with NDI in a patient with acquired immunodeficiency syndrome, who recovered completely with supportive treatment and discontinuation of abacavir.

KEY WORDS: Abacavir, acquired immunodeficiency syndrome, Fanconi syndrome, nephrogenic diabetes insipidus

Case History
A 44-year-old, homosexual male, a known patient of AIDS since the last 12 years, two months ago was started on abacavir 300 mg twice daily along with his ongoing highly active antiretroviral therapy (HAART) of lamivudine, stavudine and nevirapine by his physician, in view of progressive decline in his CD4 count and HAART resistance test result. In the past he never had any significant drug-related adverse effect.

He was hospitalized with progressively increasing generalized weakness, fatigue, anorexia, weight loss, orthostatic giddiness, muscular cramp and polyuria of two weeks duration. His clinical examination was unremarkable, except significant dehydration.

Investigations showed hemoglobin 126 gm/dl and the total leucocyte count was 4500/cmm. The differential leucocyte count and platelet count were within normal limits. Serum potassium was 2.8 mmol/L and sodium was 139 mmol/L. Serum creatinine was 104 µmol/L and urea 3.0 mmol/L. Urine was remarkable. ESR was 30 mm/hr and CRP was 1.1

Received: 25-12-05
Review completed: 16-01-06
Accepted: 06-02-06
any increase in urine osmolality, (urine osmolality remains below 300 mOsm/l of H2O) and reduction in urine volume. On ultrasound examination kidneys were of normal size and echogenicity without any evidence of urinary tract obstruction. Blood and urine electrophoresis and immunofixation did not show any evidence of plasma cell dyscrasia. On the basis of the above-mentioned clinical features and investigation findings he was diagnosed as a case of adult onset FS with NDI.

He was treated with intravenous fluid supplementation along with the replacement of potassium, phosphate, calcium, magnesium and other electrolytes along with alkali therapy. His HAART therapy was temporarily discontinued. After the initial few days of hospitalization his urine output started to decline and normalized to <2.5 liters/day, on day 8 onwards. With this supportive treatment all his electrolyte abnormalities progressively improved in the next three weeks. He was discharged from the hospital in 10 days. His electrolyte replacement was progressively withdrawn in the next four weeks. Six weeks after discharge from the hospital, his blood and urine biochemistry and electrolyte levels were within normal limits without any supplementation.

After eight weeks of discharge from the hospital, he was restarted on his HAART therapy again, first with lamivudine and stavudine without any recurrence of symptom and urinary abnormality, followed by nevirapine and abacavir. Within a week of restarting nevirapine and abacavir he had recurrence of his symptoms and developed FS and NDI again. Both nevirapine and abacavir were withdrawn and his symptoms and FS and NDI resolved in the next four weeks.

To determine the cause of his FS and NDI and optimize his HAART therapy, he was challenged with nevirapine first and abacavir later, on separate occasions. He did not develop any symptom or urinary abnormality with nevirapine but developed FS and NDI again with abacavir, which recovered completely again in the next four weeks on discontinuation of abacavir. Now after six months of follow-up, he has normal renal function without any urinary abnormality suggestive of FS or NDI and is continuing his HAART therapy without any clinical symptom.

Discussion

Abacavir is a carbocyclic nucleoside analogue, indicated for the treatment of HIV infection, which is rapidly and extensively absorbed after oral administration and gets phosphorylated to its active metabolite carbovir triphosphate, which inhibits the activity of HIV reverse transcriptase. Eighty-three per cent of drug is excreted as metabolite and only <2% is excreted unchanged in urine.[5] Nausea, headache, lipodystrophy, lactic acidosis and hypersensitivity reactions are the most frequent adverse events with abacavir.

Various studies have demonstrated that human organic anion transporter-1 (hOAT1), a basolateral membrane protein of the proximal tubule, mediates the active uptake of nucleoside analogue from the blood into the proximal tubules. From proximal tubular cells, it is secreted into the urine by multidrug resistant protein (MRP2), located at the apical side of proximal tubular cells, which is probably the rate-limited step in the secretion pathway.[6] Ho et al have shown that nucleoside analogues, adefovir and cidofovir cause nephrotoxicity by their accumulation in renal tubular cells.[7]

There is no published study on the mechanism of abacavir nephrotoxicity. The presence of FS and NDI in this particular patient suggests the probability of multiple sites of renal injury including proximal tubule and collecting duct, indicating that probably, it is not mediated by hOAT1 only, since hOAT1 is not found in collecting duct cells.

Fisher et al have reported proximal tubular dysfunction in 17% of patients with advanced HIV disease treated with adefovir.[8] Saumoy et al have indicated mitochondrial toxicity as a cause of tenofovir nephrotoxicity in HIV patients.[9]

The probability score for the development of this adverse reaction (FS and NDI) in this patient by Naranjo’s adverse reaction algorithm is 9 indicating that it is highly probable that it is due to Abacavir therapy.[10]

Although the exact pathogenesis of FS and NDI in this patient is not clear to us, the resolution of syndrome after discontinuation of abacavir and its reappearance on rechallenge, clearly indicate that abacavir is the cause of this FS and NDI.

We propose that FS and NDI are the potential adverse effects of abacavir and patients on abacavir therapy should be monitored for the early signs of FS and NDI.

References