Adefovir Dipivoxil-induced Fanconi’s Syndrome and Osteomalacia Following Multiple Bone Fractures in a Patient with Chronic Hepatitis B

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We herein present the case of a 66-year-old Japanese man with Fanconi’s syndrome. He had been receiving adefovir dipivoxil (ADV) for the treatment of entecavir (ETV)-resistant chronic hepatitis B (CHB) for four years in his 8-year treatment of hepatocellular carcinoma (HCC), but was referred to our hospital after increased levels of bone pain in his ribs, knees, and ankles. Renal dysfunction, hypophosphatemia, and increased levels of bone alkaline phosphatase were found by a hematologic test after admission for treatment of HCC. Radiography and 99mTc-labeled hydroxymethylene diphosphonate (HMDP) scintigraphy revealed multiple insufficiency fractures in the ribs, knees, ankles, and heels. After switching from ADV to tenofovir disoproxil fumarate (TDF) and treatment with calcitriol and sodium dihydrogenphosphate, the patient’s serum phosphate levels slightly increased and renal dysfunction did not improve, but after six months his clinical symptoms disappeared. To detect and prevent adverse effects from ADV, physicians and pharmacists should carefully monitor renal function and serum phosphate levels in patients with hepatitis B virus (HBV) treated for a long time with ADV.

Key words—Fanconi’s syndrome; osteomalacia; adefovir dipivoxil; hepatitis B virus; hypophosphatemia

INTRODUCTION

Adefovir dipivoxil (ADV) is a commonly used antiviral drug to treat chronic hepatitis B (CHB). Long-term ADV treatment (10 mg/d) has adverse effects, such as nephrotoxicity, Fanconi’s syndrome, and osteomalacia, especially in East Asian countries.1–4) Titration of ADV according to renal function has been established, but the best treatment for ADV-induced renal dysfunction and Fanconi’s syndrome remains unclear. The adverse effects from ADV hinder continuous treatment and lead to poor prognosis. Here, we report a case of severe bone pain from hypophosphatemic osteomalacia with Fanconi’s syndrome caused by long-term ADV treatment for a patient with CHB and hepatocellular carcinoma (HCC). A notable point of this report is that CHB was well-controlled and bone pain from hypophosphatemic osteomalacia with Fanconi’s syndrome improved after a switch from ADV to tenofovir disoproxil fumarate (TDF) and administration of phosphate and vitamin D.

CASE REPORT

A 66-year-old Japanese man who had severe bone pain involving the right-side ribcage, knees, and ankles was referred to our hospital in May 2015. The patient was diagnosed with CHB in 1983 and HCC in 2006. In July 2007, he was positive for HBs antigen, negative for HBe antigen, and positive for HBe antibody, and was started on entecavir (ETV) (0.5 mg/d) therapy. The clinical course is shown in Fig. 1(A). In September 2011, he developed ETV resistance after a 4-year period of ETV administration, and then ADV (10 mg/d) was added. The level of hepatitis B virus (HBV)-DNA was low to undetectable in November 2011. He received CHB treatment by a primary care physician and periodic treatment for HCC at our hospital. In December 2013, the patient developed pain in his knees, and celecoxib (200 mg/d) was prescribed. In August 2014, he was admitted to our hospital for periodic treatment of HCC and complained of progressive generalized bone pain involving the right-side ribcages and knees.

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The patient was 47.6 kg in weight, 153.0 cm in height, and had a body mass index (BMI) of 20.3 kg/m². His heart rate was 67 bpm and his blood pressure was 126/78 mmHg. During a physical examination, he had generalized bone tenderness, especially in the regions mentioned above. No struma were palpable. There were no specific signs in the respiratory, digestive, or circulatory systems. There was no edema in the patient’s legs. Laboratory data revealed hypophosphatemia (1.20 mg/dL; normal range 2.5–4.6 mg/dL), hypouricemia (1.70 mg/dL; normal range 3.5–7.00 mg/dL), and increased levels of alkaline phosphatase (ALP; 1389 U/L; normal range 110–360 U/L) and bone ALP (BAP; 123 U/L, normal: 13–34). The serum creatinine level was normal (1.07 mg/dL; normal range 0.60–1.10 mg/dL). However, a calculated creatinine clearance of 47 mL/min indicated renal dysfunction. The adjusted serum calcium (9.10 mg/dL; normal range 8.6–10.2 mg/dL) level was within a normal range. The patient's level of renal tubular reabsorption of phosphate (%TRP) was low at 45.4% (normal: 82–95%), indicating impairment of renal absorption of inorganic phosphate. Considering the complications of bone-related endocrine disorders that induce hypophosphatemia, we measured serum levels of intact parathyroid hormone (PTH; 39 pg/mL, normal: 10–65) and PTH-related peptide (PTHrP; <1.1 pg/mL, normal: <1.1), both of which were within the normal range. Arterial blood gas analysis revealed severe metabolic acidosis (pH, 7.32; HCO3⁻ 14.9 mmol/L; serum potassium, 3.4 mmol/L; serum sodium, 141 mmol/L; base excess, −10.0 mmol/L; anion gap 5.5 mEq/L). Urinalysis showed alkaluria (pH 7.5), proteinuria (±), glucosuria (1+), and excess excretion of amino acids (Val, 117.4 µmol/L; Ala, 3767...
There are a number of similar reports showing that ADV induces Fanconi’s syndrome and osteomalacia, but the mechanisms underlying the development of ADV-induced nephrotoxicity still remain unclear. Human organic anion transporter-1 (hOAT1), a basolateral membrane protein of the proximal tubule, mediates the active uptake of ADV from the blood into proximal tubular cells. ADV is secreted into the urine by multidrug resistance proteins (MRPs) 2, 4, and 5, which are located on the apical side of proximal tubular cells. Therefore, overexpression of hOAT1 or underexpression of MRPs may result in the accumulation of ADV in renal tubules and subsequent tubular toxicity. These findings suggest that mitochondrial toxicity of ADV and ADV-induced apoptosis of the renal tubular epithelium contribute to ADV-induced renal dysfunction.

Age (>50 years), decreasing levels of eGFR (50–80 mL/min) at the start of ADV treatment, and complications from diabetes or hypertension are risk factors for ADV-induced renal dysfunction. These risk factors may also cause ADV-induced Fanconi’s syndrome and osteomalacia.

ADV-induced nephrotoxicity is dose-dependent and reversible, which suggests that discontinuation or reduction of the ADV dose should be considered to improve serum phosphate levels and clinical symptoms. Creatinine level is a primary indicator of renal function and is used as a criterion for reducing ADV dose. The dose of ADV should be reduced in accordance with creatinine clearance (CCr) or eGFR as indicated: 10 mg/d for CCr > 60 mL/min, 10 mg/2–3 d for CCr 30–59 mL/min, 10 mg/3 d for CCr 10–29 mL/min, and 10 mg/week for CCr < 10 mL/min. In our case, ADV dose was not reduced and continued at 10 mg/d dose for 3.5 years despite the patient having chronic kidney disease (CKD) with a CCr range of 41–53 mL/min. The guidelines for the management of hepatitis B virus infection recommend that serum phosphate should be periodically measured during ADV treatment, but serum phosphate levels in the present case were not measured before the patient’s symptoms occurred.

In Japan, there are five nucleos(t)ide analogues (NA) available for CHB treatment. The first available NA was lamivudine (LAM) from 2000. ADV was adopted for patients with LAM-resistant virus carrier as the second available NA from 2004. Next, ETV was adopted in 2006 as the third NA especially for 

μmol/L). Urinary levels of β2-microglobulin (BMG, 23.51 mg/L; normal < 0.29) were also increased, but N-acetyl-glucosaminidase (NAG, 4.7 U/L; normal 0.3–11.5) was normal. These findings suggested that the patient had Fanconi’s syndrome and osteomalacia. 99mTc hydroxyethylene diphosphonate (HMDP) scintigraphy demonstrated significant abnormal uptake in the bilateral ribs, right knee, right ankle, and heel [Fig. 1 (B)]. Radiograph revealed insufficiency fractures or osteoarthritis in both knees [Fig. 1(C)]. We diagnosed the patient with osteomalacia due to Fanconi’s syndrome secondary to ADV therapy for CHB by the therapeutic course, pathogenesis, and diagnostic criteria for rickets and osteomalacia. However, we did not determine if Fibroblast Growth Factor 23 (FGF23) was related to the hypophosphatemia because we did not measure FGF23 levels. After switching from ADV (10 mg/d) to tenofovir disoproxil fumarate (TDF, 300 mg/2 d) and treatment with calcitriol (0.5 μg/d) and sodium dihydrogenphosphate (300 mg/d), the patient’s serum phosphate normalized but the patient’s renal function did not fully recover [Fig. 1(A)]. Clinical symptoms, such as bone pain, disappeared, and gait performance recovered in 6 months after starting treatment with calcitriol and sodium dihydrogenphosphate.

DISCUSSION

We treated a patient with severe bone pain from hypophosphatemic osteomalacia with Fanconi’s syndrome caused by four years of ADV treatment. His laboratory data revealed severe hypophosphatemia, high ALP, and high Cr levels. He was diagnosed with Fanconi’s syndrome induced by ADV administration. After switching from ADV to TDF, the clinical symptoms of Fanconi’s syndrome disappeared and CHB was better controlled.

Fanconi’s syndrome is caused by a functional disorder of the proximal tubule, and results in numerous symptoms, such as aminoaciduria, proteinuria, renal glycosuria, hypophosphatemia, and hyperphosphaturia. Osteomalacia is a failure to mineralize the newly formed organic matrix of bone and causes bone pain, muscle weakness, and multiple bone fractures. Loss of serum phosphate caused by Fanconi’s syndrome is one cause of osteomalacia. ADV, a nucleotide analog widely used in the management of patients with CHB, can be nephrotoxic.
NA-naive patients with strong viral load reduction and fewer resistant viruses and side effects. Because LAM-resistant viruses occur frequently and ETV has a low frequency of resistance, the first-line pharmacotherapy is usually ETV. TDF was the fourth available NA from May 2014 and improved ADV because of lower adverse events such as Fanconi’s syndrome. In February 2017, tenofovir alafenamide (TAF) was added as an improved TDF. LAM and ETV have similar resistant patterns with few severe adverse events. ADV, TDF, and TAF have similar pharmacological structures and similar adverse events. Because the first available LAM had few severe adverse events and because the adverse effects of ADV or TDF were caused by long-term administration, the present case was not diagnosed earlier.

Because ADV, TDF, and TAF have similar pharmacological structures, TDF or TAF may have adverse kidney and bone effects. The hOAT1 transporter mediates the active uptake of both ADV and TDF from the blood into proximal tubular cells, and TDF-induced Fanconi’s syndrome and osteomalacia have been reported. Thus, renal function and serum phosphate should be monitored carefully and frequently for both TDF and ADV therapies. In our case, after switching therapeutics from ADV to TDF, Fanconi’s syndrome improved and clinical symptoms, such as bone pain, disappeared. This finding was consistent with previous observations that reducing dose or withdrawal of ADV has improved ADV-induced osteomalacia. Both TDF and TAF are prodrugs of tenofovir (TFV), but TAF is more specific to target cells and TAF has less adverse effects on kidney and bone. Therefore, TAF should be used instead of TDF after switching from ADV to address ADV-induced osteomalacia in the future. Unfortunately, in this case, TAF was not available due to unreleased. Therefore, TDF was the best available therapeutic for the patient with ETV-resistant HBV. Marcellin et al. reported that TDF (300 mg/d) is more effective than ADV (10 mg/d) to treat treatment-naive patients with HBV. We decided to switch from ADV to TDF and adjust the dosage of TDF (300 mg every other day) according to renal function because, in addition to effectiveness, the expression rate of both renal dysfunction and hypophosphatemia is lower in patients treated with TDF than with ADV. In our case, a switch from ADV to TDF and administration of phosphate and vitamin D improved ADV-induced osteomalacia and controlled CHB without additional adverse effects.

In conclusion, we treated a patient with severe hypophosphatemic osteomalacia and multiple bone fractures with Fanconi’s syndrome caused by the long-term use of ADV. This is, to the best of our knowledge, the first report that analyzes the switch from ADV to TDF and treatment with calcitriol and sodium dihydrogenphosphate. The patient’s clinical symptoms markedly improved and CHB was better controlled, but the patient’s serum phosphate level remained lower than the normal range. To prevent severe adverse effects similar to the ones in this case, clinical pharmacists should work with physicians prescribing ADV, monitor renal function and serum phosphate levels, and carefully manage treatment such as suggesting appropriate doses and sharing information with patients. Pharmaceutical management by clinical pharmacists has gained attention, and cases were reported that “prepared to avoid the adverse reaction of drugs; PRE-AVOID”. Our case was an exemplary PRE-AVOID report in which we detected adverse effects, and poor outcomes were prevented by pharmaceutical management.

Conflict of Interest The authors declare no conflict of interest.

REFERENCES

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