

Low-dose adefovir dipivoxil–induced hypophosphatemia osteomalacia in five chronic hepatitis B virus–infected patients. Is low-dose adefovir dipivoxil–induced nephrotoxicity completely reversible?

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Abstract: Adefovir dipivoxil (ADV) is one of the most important nucleostide analogues currently in use for the treatment of chronic hepatitis B virus (HBV) infection. Low-dose ADV-induced nephrotoxicity in most cases was reported to be reversible after the discontinuation of ADV or by decreasing the dose of ADV. In our study, we have 5 documented cases of low-dose ADV-induced hypophosphatemia osteomalacia with or without Fanconi syndrome which were diagnosed in our hospital between 2010 and 2017. Three patients were observed to have a full recovery after the discontinuation of ADV. Two patients had persistently elevated urine β_2 -microglobulin levels and out of these two patients, one patient had persistent hypophosphatemia after the cessation of ADV. These cases illustrated that the use of low-dose ADV increased the risk of nephrotoxicity, and in some patients, low-dose ADV-induced nephrotoxicity was not completely reversible. Patients of East Asian origin, especially those with a low body mass index, were prone to a relatively higher risk of developing low-dose ADV-induced nephrotoxicity; therefore, it was worth paying attention to the side effects caused by low-dose ADV.

Keywords: hypophosphatemia osteomalacia, chronic hepatitis B virus, adefovir dipivoxil

Introduction

Chronic hepatitis B virus (HBV) infection affects approximately 240 million people worldwide,¹ and the prevalence of it in China is estimated to be at 20 million.² Adefovir dipivoxil (ADV) is one of the most important nucleostide analogues that significantly inhibits HBV replication and attenuates the progression of cirrhosis. It was approved by the US Food and Drug Administration in 2002. It is generally believed that a daily dose of 10 mg is not nephrotoxic,³ although a few cases of low-dose ADV-induced Fanconi syndrome and hypophosphatemia osteomalacia have been reported since 2008.^{3–5} The reported cases of low-dose ADV-induced Fanconi syndrome and hypophosphatemia osteomalacia have increased significantly in China since 2011.⁶ Low-dose ADV-induced nephrotoxicity in majority cases was resolved after the discontinuation of ADV or after decreasing the dose of ADV.^{5,7–9} Herein we document 5 cases of low-dose ADV-induced hypophosphatemia osteomalacia with or without Fanconi syndrome which were diagnosed in our hospital between 2010 and 2017, as

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well as a review of relevant literature on the topic. We hope to illuminate whether low-dose ADV-induced nephrotoxicity is completely reversible.

Case descriptions

Case 1

In December 2010, 68 months after the initiation of ADV treatment, a 48-year-old Chinese male presented with pain in the left lower extremity for 14 months and progressive difficulty in getting up from supine position for 3 months. He was referred to our hospital, where he subsequently had a splenectomy for the treatment of decompensated cirrhosis. He had been previously referred to the neurology and hematology department before being admitted to the endocrinology department. On physical examination, he had an abnormal waddling gait and tenderness in both hypochondria. Muscle strength was normal with tendon hyperreflexia. Laboratory studies are as illustrated in Table 1. Dual X-ray absorptiometry (DXA) (Lunar Prodigy; GE Medical Systems, Chicago, IL, USA) measurement presented in Table 2 showed low bone mineral density (BMD). Bone scintigraphy showed increased activity around multiple bones and joints. ADV was replaced by entecavir.

Three weeks after the cessation of ADV treatment, his serum phosphorus levels had increased. Seven weeks later, his symptoms and general status improved, and his serum phosphorus levels were normal. Thirteen weeks later, he no longer needed a cane while mobilizing. Twenty-two months after the cessation of ADV, his serum phosphorus level was 0.89 (0.80–1.50) mmol/L as shown in Table 1 and DXA showed that his BMD increased by 31.74% at the lumbar spine and 91.55% at the hip as shown in Table 4. His urine β_2 -microglobulin (β_2 -MG) levels were still elevated at 12281.0 $\mu\text{g/L}$ (13.0–293.0). This case had been previously published.¹⁰

Case 2

A 54-year-old Chinese female presented with tenderness in both hypochondria for 5 months and chronic back pain for 3 months. She reported progressive walking difficulties which confined her to bed, and she was referred to a pain clinic in April 2015. All the above incidents and symptoms occurred after 34 months of treatment with ADV. The laboratory studies revealed an elevated serum alkaline phosphatase level and there were no serum phosphorus levels on record. She was misdiagnosed with osteoporosis and was prescribed zoledronic acid 4 mg before

being referred to the endocrinology department. She had tenderness in her thoraco-lumbar spine and hypochondria on physical examination. She had an abnormal waddling gait. After the zoledronic acid therapy, her serum phosphorus level was 0.39 mmol/L as shown in Table 1. DXA showed low BMD as shown in Table 2. ADV was changed to entecavir in May 2015.

Two months later, she could walk with no assistance and her serum phosphorus levels had returned to normal (0.84 mmol/L). Thirteen months after the cessation of ADV, there was an increase of BMD values: 50.10% at the lumbar spine and 17.37% at the hip as illustrated in Table 4. She was asymptomatic at her 26 months follow-up, and her subsequent laboratory studies are illustrated in Table 3.

Case 3

Seventy months after the initiation of ADV treatment, a 68-year-old Chinese female presented with chronic pain on her calcaneal bone for 15 months and progressive walking difficulty for 3 months. She was subsequently referred to the endocrinology department in September 2015. On physical examination, muscle strength was normal. Laboratory studies are listed in Table 1. DXA measurement revealed low BMD as shown in Table 2. ADV was substituted to entecavir in September 2015.

Serum phosphorus levels returned to normal 3 months after the discontinuation of ADV. Five months after the discontinuation of ADV treatment, she was asymptomatic. At her 22 months follow-up, she was still asymptomatic and the subsequent laboratory data and DXA results are illustrated in Tables 3 and 4, respectively. The increase of her BMD was 41.35% at the lumbar spine and 99.57% at the hip.

Case 4

In October 2015, 120 months after the initiation of ADV, a 58-year-old Chinese male presented with chronic back pain which had been ongoing for four years. He also complained of progressive walking difficulty which confined him to a wheelchair for 15 months and subsequently he was referred to the endocrinology department. He was performed posterior 10–11 thoracic spinal canal decompression and pedicle screw fixation surgery on his spine at a local hospital in July 2013. Despite this surgical intervention, his mobility continued to deteriorate. He also noticed that he had reduced in height by 8 cm (from 170 cm to 162 cm) and he sought medical advice in July 2014. The laboratory studies at that time revealed he had low serum phosphorus levels (nadir 0.49 mmol/L), glycosuria,

Table 1 Clinical characteristics and initial laboratory studies of 5 Chinese patients with hypophosphatemia osteomalacia induced by low-dose adefovir therapy

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5	Normal range
Sex/age, years	M/48	F/54	F/68	M/58	F/73	
BMI (kg/m ²)	18.37	20.18	17.54	19.05	17.63	
Underlying diseases	CHB-related cirrhosis	CHB	CHB	CHB	CHB	
Duration of ADV to onset symptoms, months	54	28	51	72	78	
Duration of ADV to being diagnosed hypophosphatemia, months	68	34	70	105	90	
<i>Blood parameters</i>						
ALP (U/L)	297	454	223	540	249	50–135
Cr (μmol/L)	91.1	53.5	94.9	66.8	91.6	F: 45.0–84.0; M: 53.0–106.0
UA (μmol/L)	130	106	198	142	123	F: 89–357; M: 149–416
Ca (mmol/L)	2.09	2.02	2.10	2.20	2.36	2.08–2.65
P (mmol/L)	0.32	0.39	0.58	0.40	0.59	0.80–1.50
Bicarbonate (mmol/L)	20.3	NA	NA	23.9	NA	21.0–26.0
PTH (pg/mL)	74.4	83.5	27.7	40.8	39.7	15.0–65.0
25(OH) D (ng/mL)	NA	9.43	16.38	14.27	33.23	30.00
OC (ng/mL)	NA	127.90	28.34	57.02	27.76	F: 13.00–48.00; M: 14.00–46.00
β-CTX (ng/L)	NA	46.51	21.39	2114.00	735.40	F: 113.00–1008.00; M: 0.00–854.00
PINP (ng/mL)	NA	146.10	99.45	228.30	79.38	F: 20.25–76.31; M: 9.06–76.24
β ₂ -MG (μg/L)	1520	NA	NA	NA	NA	670–1500
<i>Urine parameters</i>						
Phosphorus (mmol/24 h)	32.42	3.10	5.06	7.90	15.00	
Glucosuria	Diffusely positive	Diffusely positive	Negative	Diffusely positive	Positive	Negative
Proteinuria	Positive	Positive	Negative	Positive	Positive	Negative
β ₂ -MG (μg/L)	1692.0	NA	NA	22312.3	>20000	13.0–293.0
Tmp/GFR	0.25	0.47(0.87–1.40)	0.41(0.79–1.34)	0.34	0.21(0.79–1.34)	0.89–1.34

Abbreviations: ADV, adefovir dipivoxil; CHB, chronic hepatitis B virus; BMI, body mass index; ALP, alkaline phosphatase; NA, not available; Cr, creatinine; UA, uric acid; Ca, calcium; P, Phosphorus; PTH, parathyroid hormone; 25(OH)D, 25-Hydroxy vitamin D; OC, osteocalcin; β-CTX, beta C-terminal cross-linked telopeptide of collagen; PINP, N-terminal peptide of type I procollagen; β₂-MG, β₂-microglobulin; Tmp/GFR, maximal tubular renal phosphate reabsorption normalized for glomerular filtration rate; F, female; M, male.

Table 2 Initial DXA measurement of 5 Chinese patients with hypophosphatemia osteomalacia induced by low-dose adefovir therapy

Region		Case 1	Case 2	Case 3	Case 4	Case 5
L1-4	BMD (g/cm ²)	0.649	0.483	0.757	0.634	0.740
	T-score	-4.8	-5.8	-3.1	-4.8	-3.7
	Z-score	-3.7	-4.5	-1.0	-3.6	-1.4
Femoral neck	BMD	0.398	0.511	0.579	0.501	0.657
	T-score	-5.0	-3.8	-3.3	-4.4	-2.7
	Z-score	-4.0	-2.4	-1.1	-2.9	-0.6
Total hip	BMD	0.355	0.472	0.461	0.451	0.548
	T-score	-5.7	-4.3	-4.3	-4.5	-3.6
	Z-score	-4.6	-3.2	-2.3	-3.5	-1.7

Abbreviations: DXA, dual X-ray absorptiometry; BMD, bone mineral density.

Table 3 Follow-up laboratory studies of 5 Chinese patients with hypophosphatemia osteomalacia induced by low-dose adefovir therapy

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5	Normal range
Duration of withdraw of ADV to last visit, months	22	26	22	54	18	
<i>Blood parameters</i>						
ALP (U/L)	234	102	NA	133	NA	50–135
Cr (μmol/L)	94.5	NA	83.4	56.1	NA	F: 45.0–84.0; M: 53.0–106.0
UA (μmol/L)	130	NA	101	126	NA	F: 89–357; M: 149–416
Ca (mmol/L)	2.40	2.29	2.44	2.42	2.38	2.08–2.65
P (mmol/L)	0.89	0.93	1.29	0.66	1.19	0.80–1.50
PTH (pg/mL)	74.4	NA	NA	30.6	NA	15.0–65.0
25(OH) D (ng/mL)	NA	20.96	31.73	28.91	22.09	30.00
OC (ng/mL)	NA	32.49	69.15	23.19	10.66	F: 13.00–48.00; M: 14.00–46.00
β-CTX (ng/L)	NA	807.00	363.90	657.00	235.70	F: 113.00–1008.00; M: 0.00–854.00
PINP (ng/mL)	NA	59.07	17.56	69.26	45.34	F: 20.25–76.31; M: 9.06–76.24
β ₂ -MG (μg/L)	1319	NA	NA	>20,000	NA	670–1500
<i>Urine parameters</i>						
Glucosuria	Negative	Negative	Negative	Positive	Negative	Negative
Proteinuria	Negative	Negative	Negative	Positive	Negative	Negative
β ₂ -MG (μg/L)	12281.0	75.1	107.0	2243.0	151.4	13.0–293.0

Abbreviations: ADV, adefovir dipivoxil; ALP, alkaline phosphatase; NA, not available; Cr, creatinine; UA, uric acid; Ca, calcium; P, Phosphorus; PTH, parathyroid hormone; 25(OH)D, 25-Hydroxy vitamin D; OC, osteocalcin; β-CTX, beta C-terminal cross-linked telopeptide of collagen; PINP, N-terminal peptide of type I procollagen; β₂-MG, β₂-microglobulin; F, female; M, male.

proteinuria, and a low BMD score (T score in lumbar below -2.5). ADV treatment was replaced by entecavir in July 2014, and he was on alendronate 70 mg per week because he had been misdiagnosed with osteoporosis. On physical examination, he was found to have kyphosis and tenderness in both hypochondria. He had an abnormal waging gait and he mobilized slowly. Laboratory studies are reported in Table 1. X-ray showed both a pseudo-fracture and multiple fractures. Bone scintigraphy revealed multiple increased trace uptakes in multiple bones. DXA

demonstrated a low BMD score which is illustrated in Table 2. Alendronate treatment was ceased in October 2015.

One week after the cessation of alendronate, his serum phosphorus levels increased from 0.40 mmol/L to 0.71 mmol/L. Two months after the discontinuation of alendronate, he could mobilize with no assistance. Seven months after the cessation of alendronate, he could mobilize as usual. Thirty-nine months later, his serum phosphorus levels remained at 0.66 mmol/L (they had not returned to normal). He also had high urine β₂-MG levels (>20000.0 μg/L). His

Table 4 Follow-up DXA measurement of 5 Chinese patients with hypophosphatemia osteomalacia induced by low-dose adefovir therapy

Region		Case 1	Case 2	Case 3	Case 4	Case 5
L1-4	BMD (g/cm ²)	0.855	0.725	1.070	1.466	1.037
	T-score	-3.0	-3.8	-1.2	2.0	-0.8
	Z-score	-2.1	-2.3	-0.8	3.3	0.7
Femoral neck	BMD	0.694	0.601	1.013	1.053	0.742
	T-score	-2.9	-3.1	-0.4	-0.1	-2.1
	Z-score	-1.7	-1.7	0.7	1.4	-0.4
Total hip	BMD	0.680	0.554	0.920	0.883	0.846
	T-score	-2.9	-3.6	-0.1	-1.5	-1.3
	Z-score	-2.1	-2.5	0.4	-0.5	0.2

Abbreviations: DXA, dual X-ray absorptiometry; BMD, bone mineral density.

BMD increased by 131.23% at the lumbar spine and 95.79% at the hips as shown in Table 4.

Case 5

A 73-year-old woman complained of bilateral heel pain for 1 year accompanied by progressive generalized pain, and she was then referred to the endocrinology department. She had been on ADV treatment for 90 months prior to her referral (treatment was initiated in January 2017). Physical examination was unremarkable. Laboratory studies are summarized in Table 1. DXA studies demonstrated a low BMD score as seen in Table 2. ADV treatment was discontinued in January 2017.

Two months after the discontinuation of ADV treatment, her symptoms subsided and her serum phosphorus levels were 0.93 mmol/L. After 18 months follow-up, the patient was still asymptomatic and her BMD increased by 40.14% at her lumbar spine and 54.38% at her hip.

Discussion

All 5 patients were observed to have had high urinary phosphate excretion and an initially low TmP/GFR ratio. These abnormalities indicated renal phosphate waste. According to the medical histories of these patients along with a negative family history, it was easy to link the application of low-dose ADV with secondary hypophosphatemia osteomalacia with or without Fanconi syndrome. It was noted that it took 6~33 months from the onset of symptoms to diagnosis. It is important to note that in each case, diagnosis was delayed. The reasons might be as follows. Firstly, most of the hypophosphatemia osteomalacia-related symptoms such as pain and fatigue were not specific. Secondly, serum phosphorus levels are not routinely included in blood testing panels in most Chinese

hospitals. Only two patients were referred to the endocrinology department at the onset of their symptoms. The other 3 patients were referred to the neurology and hematology departments, pain clinic and orthopedics department in which serum phosphorus levels were not routinely run, respectively. Moreover, it seemed that hypophosphatemia osteomalacia was quite easy to be misdiagnosed. They were misdiagnosed with various different diagnoses. Of these patients, patient 1 had a high suspicion of malignancy whereas patients 2 and 4 were misdiagnosed with osteoporosis.

Patients 2 and 4 were prescribed with zoledronic acid and alendronate, respectively. In case 2, after the application of zoledronic acid, the patient was observed to have severe hypophosphatemia which was reversible 2 months after the cessation of ADV. The patient had developed severe hypophosphatemia osteomalacia-related symptoms before the administration of zoledronic acid. Therefore, despite not having any initial serum phosphorus levels on record before the administration of zoledronic acid, we have hypothesized that the main reason for hypophosphatemia was due to the use of ADV, meanwhile zoledronic acid might also play a role in the deteriorating of hypophosphatemia. In case 4, after the cessation of alendronate, there was a significant change in serum phosphorus levels from 0.40 to 0.71 mmol/L. Bisphosphonates may have an effect on the mineralization of bone;¹¹ therefore, there is a need to avoid the application of bisphosphonates in patients presenting with hypophosphatemia osteomalacia. More than 150 cases of low-dose ADV-induced hypophosphatemia osteomalacia or Fanconi syndrome have been reported since 2008,^{5,11-15} the majority of which are of East Asian origin. It seems that HBV patients of East Asian origin are prone to developing nephrotoxicity on low-dose ADV, and the reasons for this may be

multifactorial. Firstly, the prevalence of HBV is high in the East Asian population; therefore, East Asian HBV patients run a high risk of exposure to ADV treatment. Secondly, people of East Asian origin usually present with a relatively low BMI. In a Japanese study, patients with low BMI were observed to have a higher risk of ADV-induced kidney proximal tubular dysfunction.¹⁶ Our patients also presented with low BMI as shown in Table 1. Finally, low-dose ADV-induced nephrotoxicity might have some genetic predisposition characteristics. For example, Zhe et al found that the G/A genotype at c.2934 of the *ABCC2* gene might be a predictor of patients at greater risk for developing ADV-associated tubulopathy in a retrospective study.⁵

After cessation of ADV and long-term follow-up, patient 1 and patient 4 were still found to have high urine β_2 -MG levels. Urine β_2 -MG is a sensitive marker of renal tubular injury.^{17,18} This indicated that proximal renal tubular function could not be completely restored in patient 1 and patient 4. In addition to elevated urinary β_2 -MG levels, patient 4 was observed to have persistently mild hypophosphatemia after long-term follow-up after the cessation of ADV. This was a rare finding in the other studies because ADV-induced nephrotoxicity in most cases was reported to be reversible. There are a few cases in the English language medium that have mentioned that ADV induced nephrotoxicity was not completely reversible.¹⁹ Dai et al reported on 2 middle-aged chronic hepatitis B men who had been on a daily dose of 10 mg ADV for more than 3 years, and who then developed Fanconi syndrome and secondary hypophosphatemia osteomalacia.¹⁹ After the cessation of ADV treatment, the symptoms were slightly alleviated but the hypophosphatemia persisted.¹⁹ It is interesting to note that the two patients who were reported to have irreversible nephrotoxicity induced by low-dose ADV were middle-aged men. In our study, patient 1 and patient 4 were middle-aged men who also developed irreversible nephrotoxicity. Could this be a coincidence or could there be a tendency toward gender predisposition? To answer this question, further large-scale studies are needed to be conducted to rule out this hypothesis.

In conclusion, we have reported 5 cases of low-dose daily ADV-induced hypophosphatemia osteomalacia in HBV patients. Nephrotoxicity was not completely reversible in 2 patients. These cases have illustrated that low-dose ADV was nephrotoxic, and in some patients, low-dose ADV-induced nephrotoxicity was not completely reversible. Patients of East Asian origin with low BMI seem to be at risk of low-dose ADV induced nephrotoxicity; therefore, greater attention needs to be paid to this group.

Ethical approval and copyright

The study was approved by the institutional ethical committee of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University. All patients in this case series provided written informed consent for the case details to be published.

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Disclosure

The authors report no conflicts of interest in this work.

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