

The Efficacy of L-Carnitine for Fanconi's Syndrome caused by Long-Term Administration of Adefovir Dipivoxil (Adv) in a Patient with Chronic Hepatitis B: A Case Report

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Abstract

A 51-year-old female with chronic hepatitis B treated by Lamivudine (LAM) and Adefovir Dipivoxil (ADV) because of breakthrough hepatitis developed hypophosphatemia. She was diagnosed with Fanconi's syndrome caused by the long-term administration of ADV. Since her symptoms did not improve after decreasing the ADV dosage and administering vitamin D, she was given L-carnitine. This led to a gradual improvement of her symptoms and the hypophosphatemia. These results indicate that a decrease in the ADV dose combined with supplementation with L-carnitine led to an improvement of Fanconi's syndrome acquired by a patient with chronic hepatitis B while taking ADV.

Keywords: Chronic hepatitis B; Adefovir dipivoxil; Fanconi's syndrome; Hypophosphatemia; L-carnitine

Introduction

An estimated 400 million people worldwide are chronically infected with Hepatitis B Virus (HBV) [1]. HBV-infected patients may develop cirrhosis and hepatocellular carcinoma [2]. Thus, the aims of HBV treatments are to achieve suppression of HBV replication and cause remission of chronic liver disease. Pegylated interferon and oral nucleoside analogues are the main therapeutic agents that have been available for treatment of HBV-infected patients in Japan [3]. Adefovir Dipivoxil (ADV) is an oral prodrug of the nucleoside reverse transcriptase inhibitor, adenine. ADV has been shown to be efficacious against both the Human Immunodeficiency Virus-I (HIV) and HBV. However, it is associated with adverse events and has been shown to exhibit nephrotoxicity, in which there is a gradual increase in creatine and a decrease in serum inorganic phosphorus and Uric Acid (UA) (Fanconi's syndrome). Even when administered at a low 10 mg/day dose, long-term ADV use has been shown to cause adverse events [4-6]. If Fanconi's syndrome due to ADV does develop, ADV administration is stopped and the patient is changed to a different oral nucleoside analogue, or ADV is continued but with a decrease in the dose from 10 mg/day to 10 mg/two days in conjunction with supplementation with phosphate and vitamin D in some cases [3]. Unfortunately, ADV cannot be discontinued in some patients due to the development of resistance to the other oral nucleoside analogues or some patients do not show the ineffectiveness of the 10 mg/two day dosage and supplementation with phosphate and vitamin D. Thus, this complication can be a major clinical problem. Fanconi's syndrome results from a generalized dysfunction of the proximal renal tubule. It has been reported that Valproate (VPA) administration can also lead to the development of renal Fanconi's syndrome [7]. Decreases in the serum total or free carnitine levels have been described in severely disabled patients who were receiving long-term tube feeding in conjunction with VPA therapy [8]. In addition, her serum total and free L-carnitine decreased to the low limit, respectively. Thus, as her symptoms did not improve after the decreased dosage of ADV, L-carnitine (1800 mg peroral (per OS)) was added on.

This case indicated that Fanconi's syndrome acquired by patients with chronic hepatitis B taking ADV at a dosage of 10mg/day was improved by the decreased dosage of ADV and L-carnitine added on.

Case Report

A 51-year-old female with chronic hepatitis B began receiving Lamivudine (LAM) treatment at the age of 44 years old. However, at one year after starting the treatment, she developed breakthrough hepatitis. As a result, her treatment was switched to LAM and ADV. After changing her treatment, there was improvement of her hepatitis symptoms. Unfortunately, six years later we observed an increase in her serum creatinine and Alkaline Phosphatase (ALP), a decrease in her serum Uric Acid (UA), and she exhibited hypophosphatemia (Figure 1 and Table 1). In addition, total and free L-carnitine decreased to 29.2 $\mu\text{mol/L}$ and 21.5 $\mu\text{mol/L}$, respectively.

She was diagnosed with Fanconi's syndrome associated with hypophosphatemia and intractable pain caused by long-term administration of low-dose ADV. Subsequently, we decreased her ADV dosage from 10 mg/day to 10 mg/two day and administered vitamin D supplementation. Since there was no improvement noted in her symptoms after the decreased ADV dosage and the administration of vitamin D, L-carnitine (1800 mg per OS) was added on. As a result of these modifications, her symptoms gradually began to change, with an increase in the serum ALP, decrease in the serum UA, and improvement of her hypophosphatemia (Figure 2). At 1, 2, 6 and 9 months, her ALP decreased from her baseline value of 748 IU/L to 738 IU/L, 670 IU/L, 563 IU/L, and 447 IU/L, respectively, while her Inorganic Phosphorus (IP) increased from her baseline value of 1.9 mEq/L to 3.0 mEq/L, 2.8 mEq/L, 3.7 mEq/L, and 3.1 mEq/L, respectively.

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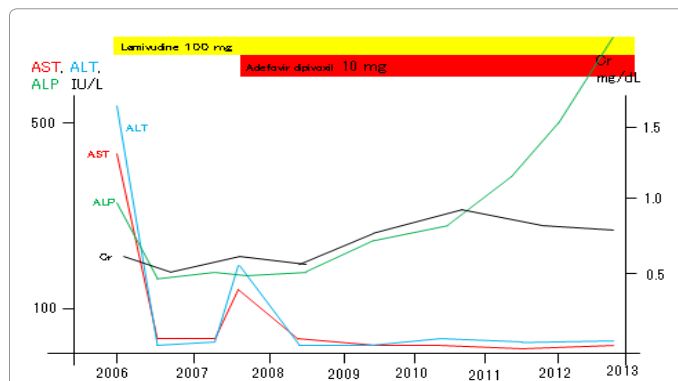


Figure 1: Clinical course of the lamivudine (LAM) treatment that was started in the patient at the age of 44 years, with the subsequent development of breakthrough hepatitis one year later. The left axis shows AST (IU/L), ALT (IU/L) and ALP (IU/L). The right axis shows Cr (mg/dL). After the administration of ADV, the ALP increased every year.

Hematology		Biochemistry	
WBC	35*102/mm3	Na	144mEq/l
	neuro 50.0%	K	3.4 mEq/l
	lym 43.6%	Cl	108 mEq/l
	eosino 1.1%	IP	1.9 mEq/l
	mono 4.5%	Alb	4.6 g/dl
		UN	11.9 mg/dl
RBC	401*104/mm3	Cr	0.87 mg/dl
Hb	12.6g/dl	UA	1.7 mg/dl
Ht	38.90%	TC	153 mg/dl
Plt	22.5*104/mm3	TG	57 mg/dl
		Glu	87 mg/dl
Urine		γ-GTP	21 U/l
Protein	(+)	ALP	748 IU/l
Glucose	(+)	ALP2	35.7
Blood	(-)	ALP3	61.7
		AST	24 IU/l
Viral Marker		ALT	20 IU/l
HBs Ag	(+)	TB	0.4 mg/dl
HBs Ab	(-)	DB	0.1 mg/dl
HBs Ag	(+)	CRP	0.05 mg/dl
Hbe Ab	(-)		
HBV DNA	2.1LGE/ml		
HCV Ab	(-)		
		L-carnitine	
Coagulation		Total	29.2µmol/l
PT	11.3 s	Free	21.5µmol/l
	(82.1% INR 1.08)	Acyl	7.7µmol/l

Table 1: Exhibited hypophosphatemia and total and free L-carnitine decreased.

In addition, her total and free L-carnitine increased from 29.2 µmol/L and 21.5 µmol/L to 71.4 µmol/L and 55.4 µmol/L, respectively (Table 2).

Discussion

ADV is known to cause Fanconi's syndrome when used to treat HIV infections at doses ranging from 60 to 120 mg/dl [4]. However, other reports have shown cases of Fanconi's syndrome in HBV patients treated with ADV at a dose of only 10 mg daily [6,9,10]. Fanconi's syndrome results from a generalized dysfunction of the proximal renal

tubule that subsequently leads to an impaired reabsorption of amino acids, glucose, UA, bicarbonate and phosphate, thereby causing an increased excretion of these solutes into the urine [11,12]. Previous reports have investigated Fanconi's syndrome in patients with chronic hepatitis B who develop complications when taking ADV and have recommended that ADV either be switched to Entecavir(ETV) or be continued after a decrease to a half dose (10 mg/two day) [3,13,14]. However, it has also been reported that after switching to ETV from LAM and ADV in patients who exhibit LAM resistance, there is a tendency for the rate of ETV resistance to also increase [15]. Therefore, we were hesitant to switch our current patient from LAM and ADV to ETV.

It has been reported that the likely mechanism for ADV nephrotoxicity is as follows. Human organic anion transporter-1 (hOAT-1), which is a basolateral membrane protein of the proximal tubule, mediates the active uptake of ADV from the blood into the proximal tubular cells. As a result, ADV is then secreted into the urine by Multi-Drug Resistant Protein (MRP2), which is located at the apical side of the proximal tubular cells [16]. Law et al. postulated that genetic defects in the involved ADV transporters could lead to overexpression of hOAT1 and/or an underexpression of MRP2, respectively. These changes subsequently lead to an accumulation of intracellular ADV in the proximal renal tubular cells [17]. A further report demonstrated that ADV caused nephrotoxicity due to its direct toxic effect on these tubular cells [18]. Thus, the accumulation of intracellular ADV in the proximal renal tubular cells may be a contributory factor responsible for the dysfunction of the proximal tubules.

On the other hand, ADV is esterified by the pivaloyloxymethyl moiety. Metabolism of this drug produces a pharmacological active site for formaldehyde and pivalic acid in the intestine. In humans, most pivalic acid binds tightly to carnitine and is excreted as pivaloylcarnitine in the urine, which can lead to a carnitine deficiency [19]. L-carnitine is essential for transportation of long-chain fatty acids

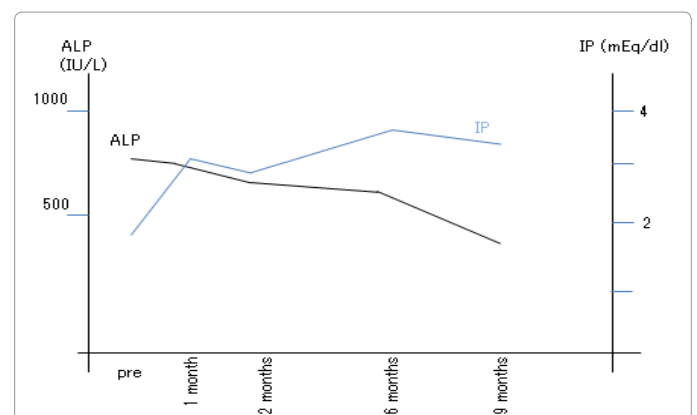


Figure 2: Clinical course after the addition of L-carnitine (1800 mg per OS). The left axis shows the ALP (IU/L), while the right axis shows IP (mg/dL). At 1, 2, 6, and 9 months, the ALP decreased from the baseline value of 748 IU/L to 738 IU/L, 670 IU/L, 563 IU/L, and 447 IU/L, respectively, while the IP increased from the baseline value of 1.9 mEq/L to 3.0 mEq/L, 2.8 mEq/L, 3.7 mEq/L, and 3.1 mEq/L, respectively.

L-carnitine	Pre-treatment	1month later
Total	29.2 µmol/ml	71.4 µmol/ml
Free	21.5 µmol/ml	55.4 µmol/ml
Acyl	7.7 µmol/ml	16.0 µmol/ml

Table 2: Free L-carnitine increased.

into the mitochondria and for fatty acid oxidation. Thus, L-carnitine plays an important role in the production of energy [20]. In addition, it is well known that L-carnitine is highly conserved, with more than 90% of the filtered carnitine reabsorbed at the proximal tubule level [21]. Therefore, we postulate that the accumulation of intracellular ADV in the proximal renal tubular cells induces an L-carnitine deficiency that subsequently causes the dysfunction of the proximal tubules due to the development of a loss of energy production.

Conclusion

In conclusion, we evaluated a patient with chronic hepatitis B who developed Fanconi's syndrome after taking ADV at a dosage of 10 mg/day and then subsequently improved after a decrease in her ADV dosage along with the addition of L-carnitine to the treatment regimen.

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