Chronic Hepatitis B with Fanconi’s Syndrome Triggered by Short-term Administration of Adefovir Dipivoxil

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Abstract

The patient was a 45-year-old man who had Down syndrome and hepatitis B virus (HBV) with a high virus load and the presence of hepatitis B e antigen. He had received lamivudine (100mg/day: per os) as nucleoside/nucleotide analogues (NAs) from April 2005 to December 2012. Although the initial response of HBV DNA was favorable, a high level of viral breakthrough without hepatitis reactivation occurred after 16 -months of lamivudine administration. In December 2012, the therapy with lamivudine was substituted with adefovir dipivoxil (ADV) and entecavir hydrate (ETV) after informed consent was obtained. Serum HBV DNA gradually decreased over 7 -months of this drug substitution; however, there was a gradual increase in the serum alkaline phosphatase (ALP) level without increase in the other hepatobiliary enzymes and nephrotoxicity. Since he was suspected as having drug-induced liver damage and nephropathy caused by NAs, ADV and ETV were administered every other day for 3 months, resulting in no improvement. The laboratory data was obtained in December 2013 as follows; peak 3 dominant in the ALP isoenzyme analysis, low levels of serum calcium, phosphorus and urinary acid, excessive urinary excretion of amino acid and increased level of serum creatinine. Thus, we suggested that he suffered from acquired Fanconi’s syndrome induced by ADV . Administration of ADV was then discontinued after 12 months of drug substitution and only ETV was prescribed. Six months after ADV discontinuation, some of the indicative markers of renal dysfunction, including Fanconi’s syndrome, were normalized and recovered to the same levels before the combined use of ADV and ETV. The patient had been treated with sodium valproate and carbamazepine for the unstable mental state and epilepsy before the lamivudine administration; however, the negative synergic action among these drugs and NAs was not evaluated sufficiently. Here, we report the earlier onset of Fanconi’s syndrome triggered by ADV, which is usually diagnosed after long-term ADV administration. We suggest that the adequate evaluation of renal function, including proximal tubular damage before administration of ADV and close observation from the early period during treatment with ADV, is required.

Key words

Fanconi’s syndrome, hepatitis B virus, direct-acting antivirus, adefovir dipivoxil.

Introduction

The recent progress in the treatment of chronic hepatitis B using nucleoside/nucleotide analogues (NAs) is remarkable. The first-line drug, lamivudine, has a major risk of early viral breakthrough; thus, another drug with more resistance to viral breakthrough is required. Nowadays, NAs therapy with either mono or combination therapy with adefovir dipivoxil (ADV) and entecavir hydrate (ETV) is used. As a
side effect of long-term ADV administration, the onset of Fanconi’s syndrome is quite rare; however, it should always be taken into consideration because its diagnosis is sometimes delayed due to a long asymptomatic period. Here, we encountered a patient with earlier occurrence of Fanconi’s syndrome triggered by ADV and assessed the clinical significance in drug side effects and its association with disease backgrounds.

**Case presentation (description)**

The patient was a 45-year old man who was previously diagnosed with Down syndrome and chronic hepatitis B in 2002. His height was 158 cm, weight 65 kg, and blood pressure 100/70 mmHg. He had no particular family history or personal history of smoking, alcohol or drug abuse, or drug allergy. Although he was fully conscious and alert, we identified mild mental retardation and unstable epilepsy accompanied by Down syndrome. He had been under primary medication at an institution for those with intellectual disabilities. No jaundice, anemia, or abnormal findings in the chest or abdomen was found. The hepatic reserve was preserved; the serial echography and computed tomography showed no signs of space-occupying region or liver cirrhosis (image is not shown). The serum creatinine (Cr) levels (1.03 mg/dl; July 2005) as the baseline of renal function was within normal range. The time course of medical therapy is shown in **Figure 1**. The patient had received lamivudine as NAs since April 2005 because chronic hepatitis B was active (alanine transaminase 388 IU/l) and hepatitis B e antigen (HBeAg) was positive. At the induction of lamivudine, the serum virus load of HBV was high (HBV DNA: 7.0 LGE/ml, TMA assay). Although the initial response of HBV DNA level was favorable, the high level of viral breakthrough (8.2 LGE/ml) without hepatitis reactivation became apparent 16 months after induction. In December 2012, after the 7-year observation, lamivudine was substituted with adefovir dipivoxil (ADV) 10 mg/day per os (PO) and entecavir hydrate (ETV) 0.5 mg/day PO for preventing hepatocellular carcinoma. After 11 -months of substitution, the serum HBV DNA levels gradually decreased (2.9 LC/ml, realtime PCR TaqMan assay). After 7 -months of substitution in the asymptomatic period, an increase in the serum alkaline phosphatase (ALP) level (390 IU/l) without increasing the other hepatobiliary enzymes, an increase in the serum Cr (1.47 mg/dl), and a decrease in the estimated glomerular filtration rate (eGFR : 43 ml/min) became apparent and gradually worsened. We presumed that the patient was having drug-induced liver damage and nephropathy caused by NAs; the dosage of ADV and ETV was reduced from a daily dose to 3 times per week 9 months after the therapy substitution, resulting in no improvement. The serum ALP levels gradually increased during the 3-month observation period (1757 IU/l at maximam), and the isoenzyme analysis in serum ALP (peak 3 dominant: December 2013) indicated that the cause of these changes might be associated with bone regeneration associated disease, hyperthyroidism, or hyperparathyroidism. The laboratory data with normal parathyroid hormone and the decreased levels of both serum calcium (Ca 8.1 mg/dl) and phosphorus (P 1.4 mg/dl, January 2014) ruled out hyperparathyroidism; thyroid function indicated mild hypothyroidism. Along with the change in the serum ALP level, the serum urinary acid (UA) level gradually decreased (1.7 mg/dl) and the renal damage slightly worsened (Cr 1.51 mg/dl, September 2013). The additional laboratory data of excessive urinary excretion of amino acids (January 2014) suggested that the patient might have Fanconi’s syndrome. **(Table 1)** The use of ADV was then discontinued 12 months after the substitution of NAs; the serum ALP, Cr, and UA levels gradually improved (ALP 419 IU/l, Cr 1.16 mg/dl, UA 3.3 mg/dl), and the serum Ca and P levels were normalized approximately 6 months after ADV discontinuation (July 2014). Simultaneously, the HBV DNA levels showed a gradual decrease (4.0 LC/ml) without hepatitis reactivation.

**Discussion**

In the present case, the clinical and laboratory data identified acquired Fanconi’s syndrome triggered by ADV in a HBV carrier with chronic active hepatitis B. The efficacy and clinical significance of ADV for HBV is generally established\(^2\), although, long-term administration can trigger Fanconi’s syndrome even under a carefully maintained dosage (10 mg/day)\(^3\), \(^4\). An earlier study published in Japan has reported that Fanconi’s syndrome is usually diagnosed an average of 5 to 6 years after the administration of ADV, and that there is a tendency for accompanying bone pain and/or pathological fracture due to osteoporosis\(^5\). It is well known that a long-term decline in serum Ca caused by Fanconi’s syndrome induces osteoporosis. Our patient only showed signs of only mild osteoporosis (data of bone density not shown) without pathological bone fracture or joint
Figure 1. Time course of medication therapy

pain. We noted that the period from the NAs substitution to the appearance of Fanconi’s syndrome was relatively short (6 months) in our case compared with the earlier reported cases⁵.

According to the change of laboratory data after the substitution of NAs, ADV was strongly suggested as the main cause of Fanconi’s syndrome. Focusing on renal damage, including Fanconi’s syndrome, we noticed that the previous treatment with carbamazepine (since 2005) and sodium valproate (since 2007) for an unstable mental state accompanied by epilepsy. The clearance route of both drugs is renal excretion, which could be associated with renal impairment. However, the renal damage indicated by serum Cr was within normal range before lamivudine administration (1.03 mg/dl, July 2005); there was no definite evidence of renal damage due to the use of carbamazepine and sodium valproate. After the initiation of lamivudine administration, no negative synergic actions in serum Cr levels were found among lamivudine, carbamazepine or sodium valproate. During this period (July 2012), we first measured serum Cr and eGFR together, and the serum Cr level was normal (1.0 mg/dl), while the eGFR showed the minimum of the normal range or mild low levels (60 ml/min).

These result suggested that renal function should be evaluated with care in cases treated with renal-excretion drugs.

A case of acquired Fanconi’s syndrome induced by sodium valproate in an adult is quite rare⁶. Although the pathogenic mechanism of proximal tubular damage in Fanconi’s syndrome induced by sodium valproate or ADV has already been reported⁶ ⁷ ⁸, we had no data related to these experimental studies in our case. We speculated that the previous treatment of sodium valproate might accelerate the earlier occurrence of Fanconi’s syndrome after the initiation of ADV administration. Throughout the course of our study, there was no data of indicative markers of proximal tubular damage (beta2-microglobulin, N-acetyl-beta-glucosaminidase); thus, latent Fanconi’s syndrome could not be retrospectively assessed in the asymptomatic period before the substitution use of ADV and ETV.

The results of this case reveal that adequate evaluation of renal function, including proximal tubular damage before administration of ADV and tenofovir, new NAs since 2014, and close observation during the administration of these drugs are necessary. In cases with renal impairment or previous administra-
tion of sodium valproate and/or renal excretion drugs, the dose control of NAs and the use of other drugs should be taken into consideration.

References


