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Case Report

Constipation during Entecavir treatment in Chronic Hepatitis B patients: Two Cases Reports

Abstract

Entecavir (ETV) is an oral nucleoside analog inhibitor of hepatitis B virus (HBV) DNA polymerase, which is widely used in patients with chronic hepatitis B (CHB). Despite the excellent safety data of this agent, the adverse events of headache, diarrhea, nausea and vomiting are recorded in the drug instruction of ETV. Here we report two CHB patients with ETV-associated constipation in whom symptom fully disappeared following ETV withdrawal.

Introduction

Entecavir (ETV) is a nucleoside analog inhibitor of hepatitis B virus (HBV) DNA polymerase, and its potent antiviral efficacy and high genetic barrier to viral resistance have been demonstrated in the long-term treatment of chronic hepatitis B (CHB) [1]. Several common gastrointestinal adverse reactions of ETV such as nausea, vomiting, indigestion and diarrhea have been reported, but constipation adverse reaction is extremely rare and no literature could be searched in Web of Science or PubMed. Here, we reported two cases of constipation during ETV treatment.

Case Presentation

Case A

A 21-year-old treatment-naïve man with HBeAg-positive CHB, without any co-morbidity or complication, was admitted to the out-patient clinic of our hospital. At the time of consultation, his alanine aminotransferase (ALT) value was 139 IU/L, HBV DNA level was high to 4,570,000 IU/mL, and his abdominal ultrasound imaging didn't report any placeholder or morphological changes in liver. According to the consensus recommendations of the Asian Pacific Association for the Study of the Liver, this patient was treated with ETV 0.5mg/day since March 2015. After 15 months of treatment, he already had undetectable serum HBVDNA, but he complained of difficulty in defecating. The defecation frequency suddenly changed from once a day to twice a week, and the amount of feces also reduced significantly as reported by patient. His physical examination was normal, and the results of general blood examinations (including blood routine test, liver

and renal function, blood fasting glucose, blood lipid and electrolyte) and serum tumor markers (including AFP, CEA, CA199, CA125 and CA50) were all within normal range. And the results of rectal speculum and capsule endoscopy examinations were also normal. This patient was also evaluated by an endocrinology physician for a possible endocrine disorder or lack of vitamin that may cause constipation; however, no evident abnormal finding was found. After comprehensive assessment, we suspected the possibility of ETV-associated constipation, so this patient was suggested to temporarily stop ETV antiviral therapy. Interesting, his difficulty defecating obviously alleviated since the 2nd day after ETV withdrawal, and constipation appeared again when he tried to take ETV again. Thus, ETV-associated constipation was diagnosed, and the patient was managed by switching ETV to tenofovir disoproxil (TDF) at a dose of 300mg once daily. Besides the continued biochemical and virological responses, the constipation gradually alleviated and completely disappeared after the second week of TDF treatment.

Case B

A 45-year-old man diagnosed with HBeAg-positive CHB was treated with ETV 0.5mg/day plus adefovir dipivoxil (ADV) 10mg/day following an initial failure ADV treatment (rtN236T). And the combination treatment of ETV plus ADV was started in January 2016. While on the first 3 months of combination treatment (ADV+ETV), no complaint was reported, and his elevated ALT had returned to normal and serum HBV DNA had become undetectable (<100 IU/mL). However, at the end of the fourth month of combination treatment, he felt obvious difficult defecation without apparent willingness to defecate.

Thus, he received some intervention measures for promoting defecation (including traditional Chinese herb medicine and acupuncture treatment), but his constipation was not obviously alleviated. Just as above patient (case 1), he then received physical examination, general blood examinations, serum tumor markers, rectal speculum as well as capsule endoscopy screening, and an endocrinology physician was also consulted; however, no evident abnormal finding was found. Based on the experience acquired from Case 1, we highly suspected the constipation was also caused by ETV. After we informed the patient about the ETV's possibility for causing constipation and obtained his agreement, the ETV was replaced by lamivudine (LAM) 100mg/day. After switching to ADV+LAM for just one week, his difficulty defecating was completely disappeared, and constipation didn't happen again until now. Additionally, his serum HBV DNA remained persistently undetectable, liver and renal function remained within the normal range since switching to ADV+LAM combination therapy.'

Discussion

Although nucleos (t) ide analogues and peginterferon alfa are approved for the treatment of CHB, these agents are not without adverse reactions [2-4]. ETV has previously been reported to be associated with the adverse reactions such as headache, fatigue, nausea, decreased libido, etc, [3-5]. In the presented cases, both of the patients reported constipation, which occurred during the treatment course of ETV and disappeared after ETV withdrawal. To our knowledge, this is the first report of ETV-associated constipation. As the feature of highly potent against HBV replication with low rate of drug resistance, ETV has been recommended as the first-line oral antiviral treatment of CHB. However, its safety issues cannot be ignored in long-term real-life clinical practice. For unexplained clinical signs and symptoms occurring in the process of antiviral therapy, doctors should be aware of the possibility of adverse drug reactions.

It is well-known that when a patient receives a medication and subsequently develops an adverse drug event, the physician and patient are faced with the complex task of determining whether or not a causal relationship exists [6]. In the presented cases, before considering a diagnosis of ETV-

associated constipation, the known causes of constipation were carefully evaluated. For example, the detailed information of stressful life events and disordered eating behaviors, use of other drugs and coexisting diseases were asked; and the physical examination, blood tests (including tumor markers and hormone levels) as well as intestinal endoscopy were all performed. After these potent possibilities had been ruled out, ETV-associated constipation was suspected legitimately. In fact, the disappearance of constipation after ETV withdrawal and reappearance of constipation after ETV continuance further confirmed our speculation. However, the mechanism of constipation associated by ETV is unknown, and related basic researches should be carried out to clarify it.

In conclusion, these two cases give emphasis to the safety of ETV in the treatment of CHB. ETV may cause constipation problem, and constipation could be disappeared after ETV withdrawal (switching to another antiviral agent). However, because of the limited number of patients, further studies are required to confirm this adverse event of ETV.

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