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Continuous Venovenous Hemodiafiltration for Hyperlactatemia Caused by Telbivudine in a Patient with Chronic Hepatitis B

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Abstract: Though telbivudine has been reported causing myopathy and elevating creatine kinase (CK), there is still few reports on telbivudine and hyperlactatemia in patients with chronic hepatitis B. Here we report the first case of hyperlactaemia during telbivudine treatment. A 26-year-old Chinese origin man has been received telbivudine antiviral treatment for chronic hepatitis B since 3 July, 2011, and found the CK was 68 U/L before the anti-viral treatment. After 3 months of therapy, he generally felt nausea and vomited frequently. The CK checked in local clinic was up to 222 U/L (upper limit of normal 170 U/L). However, he did not visit his doctor or stopped telbivudine treatment until he felt sore in muscles all over the body. By then, the level of CK had increased to 4151 U/ L just one year after the use of telbivudine. Even after withdrawal of telbivudine, myalgia exacerbated and CK decreased deadly slowly. Constant myolysis was developed into hyperlactatemia, finally he recovered by successfully continuous venovenous hemodiafiltration. The case findings first suggested that telbivudine might lead to high level of CK and hyperlactatemia could occur if telbivudine was not stopped immediately when CK increased evidently. Besides, it is emphasized that the serum CK and lactate acid should be monitored closely during the treatment of telbivudine.

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1. Introduction

Telbivudine is a new synthetic nucleoside analogue licensed by the US Food and Drug Administration (FDA) in October 2006 at a dose of 600 mg/d. Due to its specificity for hepatitis B and less viral resistance, telbivudine is now widely prescribed with satisfactory efficacy and safety. Recent reports indicated telbivudine facilitates elevated creatine kinase (CK) ((i.e., > 7 times upper limit of normal)) and myopathy. However, no reports mentioned hyperlactatemia caused by telbivudine monotherapy so far.

Herein, we firstly presented the clinical course of a 26-years-old Chinese man who developed into severe hyperlactatemia while he was treated with telbivudine for chronic hepatitis B (CHB), and discuss the pathophysiology, clinical features during the treatment. He finally recovered after Continuous of Venovenous Hemodiafiltration (CVVHDF).

2. Case Report

The patient，a 26-year-old Chinese man, was suffered from Hepatitis B e antigen (HBeAg) positive in 1997. He began Interferon (IFN) treatment due to elevated alanine aminotransferase (ALT) as 155 U/L (normal range: 3–35 IU/L) and HBV DNA as 1.61×10^6 copies/mL on 25 Dec. 2008. The treatment lasted for one year. But after withdrawal of IFN, the level of ALT and HBV DNA bounced to 312 U/L and 9.21×10^6 copies/mL respectively on 16 Sep. 2010. As a result, he kept on IFN treatment for six months. However, the level of ALT and HBV DNA raised again after the therapy on 20 June 2011. So he has been given telbivudine 600 mg/d since 3 July 2011.

After three months of telbivudine monotherapy, he had muscular weakness in both extremities and mild anorexia. Creatine kinase (CK) increased to 222 U/L (upper limit of normal 170 U/L) at the same time. Nevertheless, he did not complain the symptoms to his doctor and then continued the

therapy. On 5 July 2012, he was admitted for progressive myalgia. Serum tests revealed an elevation of CK (4151 IU/L), a normal ALT (29 U/L) and HBV DNA level ($<1\times10^2$ copies/mL). Telbivudine was stopped immediately, but the symptoms, including vomiting, anorexia and myalgia, were not relieved. The serum lactate level was as high as 7.3 mmol/L at admission and increased to 7.5 mmol/L the next day. The patient was then transmitted to medical intensive care unit (MICU) at once.

Serum lactate declined to 5.6 mmol/L after rehydration and alkalization on the first day in MICU. During the following day, the lactate level rebounded to 11.3 mmol/L though serum CK level dropped to 2393 U/L. The disease rapidly deteriorated made the patient could not eat by himself. His heart rate increased from 92 beats/min to 130 beats/min, mean arterial blood pressure decreased from 75 mm Hg to 60 mmHg and respiratory rate increased from18 to 30 breaths/min with diuresis simultaneously (3000-4000 mL/24 h) in spite of normal kidney function.

On the second day in MICU, hyperlactatemia was diagnosed (lactate 11.3 mmol/L) and CVVHDF was performed with a Prism flex device. We used polysulfone hollow-fiber hem filters with a surface area of 1.2 m^2. Blood flow rate was maintained between 150 and 250 mL/min according to the targeted ultrafiltration rate. Bicarbonate-based replacement solutions to maintain fluid balance were infused with pre-displacement liquid 2000 mL/h, post-displacement liquid 500 mL/h, dialysate liquid 2000 mL/h. CVVHDF was used for 15 days continuously until serum lactate was lower than 3.0 mmol/L. The changes in serum levels of lactate, CK and MGB during CVVHDF were showed in Figure 1. Vomiting and anorexia were alleviated gradually, but myalgia was difficult to be relieved. After CVVHDF discontinuation, serum lactate was below 2.8 mmol/L. Other treatments included complete bed rest, intravenous fluid rehydration and alkalization, enteral and parenteral nutrition, and so on. Blood chemical values during the telbivudine treatment were described in Table 1.

Table 1 Blood chemical values before, during (July 2011 to July 2012) and after telbivudine treatment in the described patient.

Parameter	Reference value	10.12.08	14.4.09	24.4.10	16.9.10	18.12.10	20.6.11	26.9.11	17.3.12	05.07.12	9.7.12	13.7.12	21.7.12
leucocyte	4.0-10.0/nl	4.55	3.49	4.63	5.3	4.61	4.86	4.42	5.23	4.59	6.51	4.26	6.96
thrombocyte	100-300/nl	161	182	182	158	169	172	163	173	161	169	176	142
GOT	8-40U/l	75	28	28	176	19	73	28	29	124	60	59	33
GPT	3-35U/l	155	32	46	312	15	121	27	19	29	25	32	43
Creatinine	0.57-2.08mg/dl	1.08	1.03	1.05	0.82	0.93	1.01	1.02	0.96	0.86	0.88	0.89	0.86
CK	24-184U/l	60	100	58	62	60	68	222	336	4151	1566	755	90
CK-MB	0-24U/l	5	5	8	9	8	7	9	12	18	20	16	8
MGB	0-70U/l	12	30	30	29	26	36	37	60	732	296.5	150	41.5
HBV DNA	<100	$1.6*10^6$	<500	$2.5*10^7$	$9.2*10^6$	<100	$3.9*10^4$	<100	<100	<100			<100

GOT: glutamate-oxalate transaminase, GPT: glutamate-pyruvate transaminase, CK: Creatine-kinase, CK-MB: Creatine Kinase-MB, MGB: myoglobin.

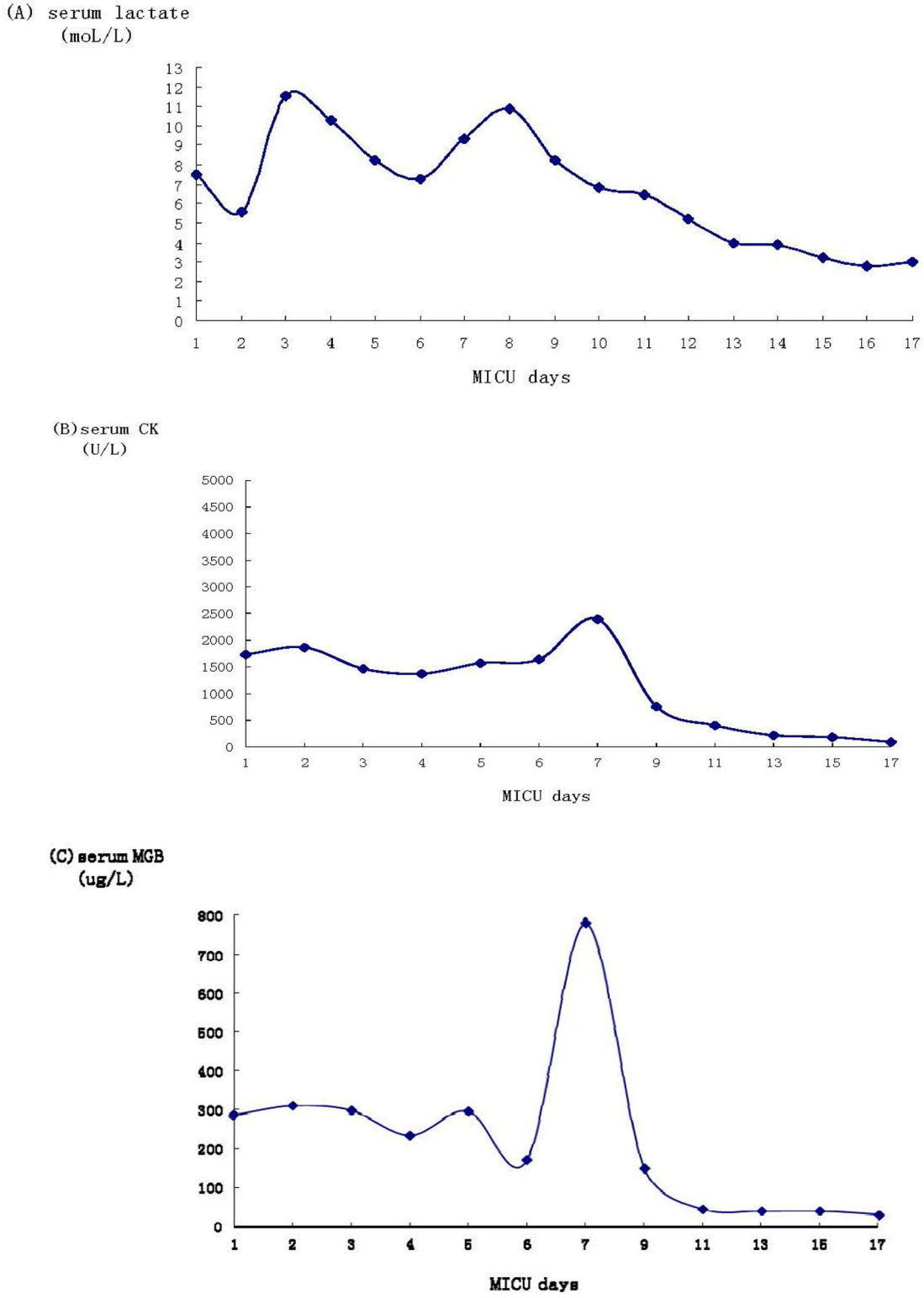

Figure 1: (A) The patient's serum lactate level was decreased gradually from 12.5 mol/L to 2.8 mol/L during CVVHDF treatment. (B) The serum CK level was from 4161 U/L to 90 U/L in MICU days. (C) The serum MGB level was from 296 ug/L to 32ug/L in MICU days.

3. Discussion

Telbivudine is a novel, administered oral nucleoside analog for CHB. It is licensed by FDA in October 2006. The multinational GLOBE trial investigated that telbivudine 600 mg/d (n = 680) had greater antiviral efficacy than lamivudine 100 mg/d (n = 687) over 2 years in CHB patients. It is proved that telbivudine had an excellent safety and tolerability profile [1]. In Chinese CHB patients, Jinlin Hou et al. found that telbivudine (for 52 weeks) provided greater antiviral and clinical efficacy than lamivudine, but less resistance [2]. However, the GLOBE trial also observed that higher incidence of grade 3 to 4 serum CK elevation (7 times of normal upper limit) in telbivudine-treated compared to lamivudine-treated patients at 2 years (12.9 % versus 4.1 %) [1]. In 200 patients using telbivudine for CHB, Zou et al. concluded the clinical features and risk factors associated with CK elevation and myopathy [3]. Some reports indicated a positive correlation between myopathy and telbivudine treatment for patients with CHB [4, 5, 6]. There were some cases of severe lactic acidosis during entecavir treatment [7, 8], but there was no report about hyperlactatemia caused by telbivudine treatment for patients with CHB.

Telbivudine is a beta-L-nucleoside analogue, which incorporates into HBV-DNA and results in DNA chain termination that pharmacologically inhibits the polymerase activity of HBV; leading to reduction of viral replication and decrease in serum HBV DNA levels [9]. Telbivudine may have a low level of activity against the human mitochondrial DNA (mtDNA) polymerase gamma causing mitochondrial loss or dysfunction, which might lead to myopathy and lactacidosis [10]. But in vitro studies indicated that telbivudine had no effect on lactic acid production, mitochondrial DNA content, or morphology [11]. At present, the biological mechanisms for telbivudine associating with myopathy and lactacidosis are still not clear. The patient had no experience of heavy exercise or heavy drinking, and had no history of diabetes mellitus. There was also no clinical or laboratory evidence of myasthenia gravis, inclusion body myositis, autoimmune disease or paraneoplastic syndrome. We supposed telbivudine might be related with hyperlactatemia in this case.

Treatments for hyperlactatemia or lacticacidosis caused by drugs include supportive care, activated charcoal, bicarbonate infusion, hemodialysis, or continuous venovenous hemofiltration. Seldom published papers mentioned the management of drug-associated lactic acidosis, most of which focused on metformin-associated lactic acidosis (MALA) and antiretroviral therapy on HIV [12, 13, 14]. Renal replacement therapies, including conventional hemodialysis and continuous venovenous hemofiltration, have been successfully employed in MALA [14, 15, 16]. We adopted CVVHDF to help our patient to eliminate the serum lactate. The result was promising and the level of the serum lactate decreased gradually after 15 continuous CVVHDF. Most of his symptoms disappeared.

4. Conclusions

The case showed that long-term therapy of telbivudine could bring on myopathy. If telbivudine is not stopped in time, hyperlactatemia might ensue. Before beginning antiviral treatment for CHB, patients should be told about the therapy's potential adverse effects, such as fatigue, limbs soreness and myosalgia etc., and then visit their physicians regularly, especially when they feel any discomfort. Apart from an inquiry of important symptoms, it should be kept in mind that laboratory test of serum muscle enzymes is required for such group. CVVHDF may be an efficient therapy for hyperlactatemia.

Consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Conflict of Interest:

The authors declare that they have no competing interests

Authors' contributions

Yan-Hong Wang carried out the clinical examination of the patient and was a major contributor in writing the manuscript. Ben-Quan Wu analyzed and interpreted the patient data regarding the hyperlactataemia. Hong-Tao Li performed the lactate level examination and interpreted the data regarding CVVHDF therapy. Liu Hui performed the serum test of the patient and the modification of the manuscript. All authors read and approved the final manuscript.

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