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RAPID COMMUNICATION

Clinical features of adverse reactions associated with telbivudine

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Abstract

AIM: To analyze the clinical features and risk factors of adverse reactions associated with telbivudine.

METHODS: Clinical data were collected from cases that presented with serious adverse reactions to telbivudine. We analyzed general information and medicine status, clinical features, results of examination, and misdiagnosis.

RESULTS: Out of 105 patients who were treated with telbivudine for hepatitis B in an outpatient department from January, 2007 to January, 2008, five presented with serious adverse drug reactions. Most of these five patients had used other nucleoside analogues in the past. Four were treated with a combination of telbivudine and interferon or another nucleoside analogue, while the other received an increased dose of telbivudine. The main adverse reactions were myalgia and general weakness. This was accompanied by cardiac arrhythmia in one patient, and nervous symptoms in three. Serum creatine kinase was elevated. The rate of misdiagnosis was high.

CONCLUSION: The adverse reactions were related to telbivudine, but the biological mechanism of the reactions is not yet clear. Combination therapy with interferon or another nucleoside analogue and a high dose may increase the risk of adverse reactions.

Key words: Adverse drug reaction; Hepatitis B; Mitochondria; Nucleoside analogue; Telbivudine

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INTRODUCTION

Telbivudine is a new synthetic nucleoside analogue[1]. Since it came on the market in October, 2006, it has been a new option for clinicians in treating chronic hepatitis B, because it significantly suppresses hepatitis B virus (HBV) replication. In our recent clinical practice, however, adverse reactions associated with telbivudine have been increasing. To understand this better, we retrospectively analyzed the clinical records of patients taking telbivudine. We hope that the result will provide clinic references for the future safe use of telbivudine.

MATERIALS AND METHODS

Subjects

Of 105 patients who were treated with telbivudine for hepatitis B at an outpatient department from January, 2007 to January, 2008, five presented with serious adverse reactions.

Methods

A retrospective method was employed to analyze the medical records of the five patients, including: general information, medicine history, telbivudine treatment, dosage, combined medication, time of occurrence and clinical features of adverse reactions, possible misdiagnosis, as well as results of laboratory tests, such as routine blood analysis, myozyme, liver function, and kidney function.

RESULTS

General information and medication status

All patients were male with an age range of 25-45 years, and a mean of 34 years. Four patients were infected with

Table 1 General information and medication status

Case	Age (yr)	Hepatitis history (yr)	Current diagnosis	Medication history	Telbivudine		Drug and time combined
					Dosage	Time (mo)	
1	45	10	Hepatocirrhosis	DLAM, ECV	600 mg *bid*	2	-
					600 mg *qd*	5	ADV for 5 mo
2	35	6	Hepatitis B	LAM, ADV	600 mg *qd*	7	Interferon for 3 mo
3	37	37	Hepatitis B	LAM, ADV	600 mg *qd*	1	-
4	30	1	Hepatitis B	-	600 mg *qd*	7	Interferon for 3 mo
5	25	2	Hepatitis B	ADV	600 mg *qd*	9	Interferon for 3 mo

LAM: Lamivudine; ADV: Adefovir; ECV: Entecavir.

Table 2 Clinical symptoms of telbivudine-related adverse reactions

Case	Occurred time (mo)	Injured location	Soreness		Weakness		Numbness		Neuralgia		Cardiac arrhythmia	
			Take	Stop	Take	Stop	Take	Stop	Take	Stop	Take	Stop
1	1.5	Shoulder	+		++		-		-		-	
	2	Limb	+	-	+	-	-	-	-	-	-	-
2	5	Limb	++	+	++	+	++	+	++	+	-	-
3	0.5	Limb	++	-	++	+	++	+	-	-	++	+
4	2	Limb	+	-	+	-	++	+	-	-	-	-
5	1	Buttock	++	+	++	+	++	+	-	-		-

++: Very serious; +: Serious; –: Not serious.

Table 3 Blood tests results

Case	Muscle enzymes		Liver function			Blood counts		Kidney function		
	CK (IU/L)	LDH (IU/L)	ALT (IU/L)	AST (IU/L)	GGT (IU/L)	WBC ($\times 10^9$/L)	HGB (g/L)	PLT ($\times 10^9$/L)	BUN (mmol/L)	CR (μmol/L)
1	438.7	182.9	97.3	216.4	115.8	4.28	144	39	3.91	101
2	900	-	32.1	31.3	24.8	2.7	130	118	2.53	107
3	191	117	32	24	26	7.19	153	212	8.38	100
4	311	253	50	47	117	3.6	147	86	4.60	45
5	400.2	424.8	92.9	68.3	21.6	3.4	133	154	-	-

HBV after birth and one acquired the infection directly during pregnancy. One patient had been diagnosed with liver cirrhosis, and the other four with chronic hepatitis B. Four were given other nucleoside analogues before telbivudine. The duration of treatment with telbivudine varied from 1 to 9 mo. In case 1, whose dosage was changed from telbivudine 600 mg twice daily alone in the first 2 mo, to 600 mg once daily in combination with adefovir for 5 mo because of the incidence of myopathy. Cases 2, 4 and 5 were treated with a combination of telbivudine and interferon (Table 1).

Clinical features of adverse reactions

Occurrence of adverse reactions varied from 0.5 to 5 mo after treatment. Myalgia was most commonly observed, mainly of the limb skeletal muscles, companied by general weakness. There were four cases with nervous damage which included symptoms of numbness, while one case had neuralgia. One case presented with cardiac arrhythmia. After telbivudine treatment was discontinued, myalgia was reduced to a varying extent, but cardiac and nervous system symptoms persisted for a long time (Table 2).

Laboratory tests

Serum creatine kinase (CK) was elevated. There was no direct correlation between CK level and severity of fatigue. Liver function was not impaired. All blood cell counts were normal except that platelets were decreased in case 1 due to hypersplenism. Neither bone marrow inhibition nor kidney toxicity was observed (Table 3).

Initial diagnosis, misdiagnosis and confirmed diagnosis

Misdiagnosis commonly took place because clinicians failed to recognize the adverse reactions. As a result, the patients had to endure further examinations and incurred the associated extra medical expenses (Table 4).

DISCUSSION

To date, there have been no special reports about telbivudine-related adverse reactions in the literature. In this investigation, the following suggested that the adverse events reported were related to treatment with telbivudine: (1) patients did not present with obvious adverse reactions to interferon or other nucleoside analogues in the past; (2) adverse reactions occurred after taking telbivudine and were reduced or resolved after discontinuing treatment; and (3) the ratio for the occurrence of adverse reactions was approximately 1:20 (5:105), which was high.

Table 4 Diagnosis process

Case	Confirmed time	Misdiagnosis	Examinations	Medication
1	1 d	Arthritis	No	Paste for arthritis
	2 d	Myocarditis	Cardiac enzymes	-
2	3 mo	Neuritis, arthritis	Lumber spinal MRI, laboratory examination	Vitamin B
3	0.5 mo	Neuritis, myocarditis	Myozyme, holter, ECG, ultrasoundcardiography	Mecobalamin, propafenone
4	1 d	-	-	-
5	2 mo	Neuritis	-	Vitamin B

Possible mechanisms of telbivudine-associated adverse reactions

Telbivudine, as a new synthetic analogue of thymidine, is phosphorylated by host cellular kinases to telbivudine-5'-triphosphate, which has a half-life of 14 h *in vivo*. Telbivudine-5'-triphosphate is then incorporated into HBV DNA by HBV polymerase, through competition with thymidine-5'-triphosphate, the natural substrate. Once inserted, telbivudine-5'-triphosphate causes DNA chain termination, thereby inhibiting HBV replication[2-4].

Some studies[5-8] have indicated that telbivudine treatment has considerable clinical efficacy, was and is well tolerated at all doses (25, 50, 100, 200, 400 and 800 mg/d), with no dose-related or treatment-related clinical or laboratory adverse events. However, other research has shown[9] that 3/680 patients treated with telbivudine presented with myopathy. However, our study is different.

At present, the biological mechanism of telbivudine-related adverse reactions is not yet clear. Given that the adverse reactions involve multiple organs, including muscle, nerves and the heart, we suggest that the mechanism is associated with cell energy metabolism. Mitochondria are involved in the production of energy. They contain many important proteins, enzymes and carriers that participate in energy transduction. Deficiency in any of these leads to a poor substrate supply for oxidative phosphorylation, and eventually to inadequate manufacture of the energy molecule ATP[10], and this causes mitochondrial disease. Organs that are highly dependent on ATP, such as the nervous system, skeletal muscle, myocardium, retina and pancreas are the most vulnerable to mitochondrial dysfunction. Symptoms of pathological conditions often take place in related areas. Clinically, skeletal muscle is a frequent target and symptoms include fatigability, weakness, as well as myalgia in 50% of cases, and CK level is not elevated significantly[11]. ATP deficiency in the heart may result in cardiac arrhythmia, dilated cardiomyopathy, or unexplainable cardiomyopathy; while deficiency in the nervous system can lead to peripheral neuropathy. It has been suggested that muscle biopsy and chromosome examination are beneficial for the diagnosis of mitochondria disease[12-14]. There is no mature experience as to the treatment at present[15-18].

The possible links between telbivudine and mitochondrial disease are as follows. (1) Mitochondrial toxicity[19-22] is a serious adverse reaction associated with nucleoside analogues, which can inhibit mtDNA polymerase-γ, then interfere with energy transduction in mitochondria. Some nucleoside analogues such as adenine arabinoside and acyclovir can cause mitochondrial toxicity[23]. (2) As a competitive substrate of natural thymidine, telbivudine is phosphorylated by host mitochondrial thymidine kinases to telbivudine-5'-triphosphate, and thymidine kinases are extensively exhausted. As a result, the normal energy transduction process is disturbed. (3) In the process of phosphorylation, high levels of phosphates are captured, which leads directly to exhaustion of ATP, which results in poor energy supply.

Although the telbivudine-related adverse reactions could not be definitely diagnosed as mitochondrial disease without a muscle biopsy and DNA study, the symptoms were identical to those of mitochondrial disease. This reminds us to pay close attention to it along with telbivudine treatment in future practice.

Risk factors related to telbivudine treatment

In case 1, symptoms of myalgia intensified following treatment with 600 mg telbivudine twice daily, while the symptoms became milder at lower doses. This suggests that myalgia is dose-dependent. Other studies[24-27] have shown that telbivudine plasma concentration is correlated with dosage when in the range 200-600 mg/d. As a result of the long half-life of this drug, a dose of 600 mg twice daily may lead to drug accumulation. Therefore, the risk may increase with higher doses.

Synergistic effect of drug combinations

Among the patients with adverse events mentioned above, three were given combination treatment with telbivudine and interferon. Although the therapeutic mechanisms of the two drugs are different[28-30], they share a common feature in causing myalgia as an adverse reaction[31]. Synergistic effects can happen when two drugs are used at the same time. It is known that most nucleoside analogues are metabolized in the kidney. According to the literature[1], plasma concentration of drugs may be elevated, if it is combined with other drugs secreted through kidney proximal tubular or altered of kidney proximal tubular function. Overall, combination therapy consisting of two or more nucleoside analogues may increase their plasma concentration, lead to a higher risk of adverse events.

Although there was no direct proof of telbivudine inducing mitochondrial disease in our study, we demonstrated that the adverse reactions were associated with telbivudine. This emphasizes that we ought to exercise caution when using telbivudine to treat hepatitis

B. First of all, practitioners need to be aware of possible adverse reactions, and inform the patient before prescription. Secondly, if telbivudine is prescribed, practitioners need to pay close attention to relevant symptoms and physical signs. Lastly, once the symptoms have been observed, an immediate medical response should be initiated. Diagnosis should be made as soon as possible, and drug therapy discontinued if necessary. Only in this way can telbivudine be used safely and effectively in clinical practice.

COMMENTS

Background

Telbivudine is a new synthetic nucleoside analogue. Since it came on the market in October, 2006, it has been a new option for clinicians to treat chronic hepatitis B, because it significantly suppresses replication of hepatitis B virus (HBV). There has been no special report about telbivudine-related adverse reactions to date, except in clinical trials.

Research frontiers

According to the results of clinical trials, myopathy, one of the telbivudine-associated adverse reactions, was found in 3/680 patients.

Innovations and breakthroughs

In the present study, the occurrence ratio of telbivudine-related myopathy was approximately 1:20 (5:105), which is different significantly different from the above result.

Applications

The study reminds us of the importance of adverse reactions when using telbivudine to treat hepatitis B. Once the symptoms are observed, doctors can diagnose the condition and initiate an immediate medical response as soon as possible, so as to relieve pain.

Terminology

Nucleoside analogues are synthetic nucleosides, which are phosphorylated in host cells, then incorporated into virus DNA instead of the natural nucleoside. Once inserted, they cause virus DNA chain termination, and therefore, inhibit virus replication. Nucleoside analogues can inhibit mtDNA polymerase-γ, and then interfere with energy transduction in mitochondria.

Peer review

The interest of the study is in the description of telbivudine-related adverse reactions during clinical practice, which may be different from those reported during clinical trials characterized by strict patient selection.

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