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CASE REPORT

Drug interaction of boceprevir and amlodipine in a patient with hepatitis C: A cardiovascular follow-up

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ABSTRACT

Boceprevir is a NS3/4A hepatitis C virus (HCV) protease inhibitor, used in combination with peginterferon and ribavirin to treat HCV. Boceprevir undergoes extensive metabolism via cytochrome P450-mediated oxidation and ketoreduction by cytosolic aldo-keto reductases. Amlodipine has been used for the treatment of patients with hypertension and also metabolised through cytochrome P450 pathway. Here, we presented a case of boceprevir and amlodipine interaction in a patient with chronic HCV and her echocardiography and electrocardiographic follow-up results. *J Microbiol Infect Dis 2015;5(1): 32-35*

Key words: Amlodipine, boceprevir, drug ınteraction,

Hepatit C virüs enfeksiyonu olan hastada boceprevir ve amlodipin ilaç etkileşimi: Kardiyovasküler Takip

ÖZET

Boceprevir, Hepatit C virüs (HCV) enfeksiyonunun tedavisinde peginterferon ve ribavirin ile kombine edilerek kullanılan NS3/4A HCV proteaz inhibitörüdür. Boceprevir, büyük çoğunlukla sitokrom P450 ilişkili oksidasyon ve sitozolik aldo-keto redüktaz ile ketoredüksiyon yoluyla metabolize olur. Amlodipin hipertansiyonu olan hastaların tedavisinde kullanılmaktadır ve amlodipin de sitokrom P450 yoluyla metabolize olur. Bu yazıda, boceprevir ve amlodipin kronik HCV enfeksiyonu olan bir hastadaki etkileşimini ve bu hastanın ekokardiyografik ve elektrokardiyografik takip sonuçlarını sunduk.

Anahtar kelimeler: Amlodipin, boceprevir, ilaç etkileşimi

INTRODUCTION

Boceprevir is an NS3/4A hepatitis C virus (HCV) protease inhibitor, used in combination with peginterferon and ribavirin to treat HCV.[1] Boceprevir undergoes extensive metabolism involving both cytochrome P450 (P450) CYP3A4/5-mediated oxidation and ketoreduction by cytosolic aldo-keto reductases 1C2 and 1C3.[2] Drug-drug interactions is particularly challenging in the treatment of chronic HCV, especially when the concomitant medications commonly prescribed for this population who have different stages of disease, including cirrhosis, organ transplantation, and coinfection with human immunodeficiency virus (HIV) are considered.[3] Amlodipine has been used for treatment of patients with hypertension and especially its combination with valsartan is advised for hypertensive patients in international guidelines whose blood pressure (BP) is more than 20/10 mmHg above the goal.[4,5] Amlodipine is mostly metabolised through hepatic cyto¬chrome P450 (CYP)3A4 enzyme system[6] so, interaction of amlodipine with drugs dealing with CYP3A4 pathway should always be in mind for possible potentiating of its antihypertensive effect. Here, we reported boceprevir and amlodipine interaction in a patient with chronic HCV who experienced hypotension with combined usage and recovered after removal of amlodipine.

CASE REPORT

Fifty-nine years old female was diagnosed with cirrhosis due to HCV and she had also hypertension

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properly regulated with fixed-dose combination of 160 mg valsartan and 5 mg amlodipine without revealing any side effects for nearly three years. HCV RNA level was 6300000 IU/ml with genotype 1. After lead-in treatment; peginterferone alfa 2b 100µg/week subcutanous + ribavirine 1000 mg/day & boceprevir 2400mg/day treatment were started. Pretreatment and follow-up electrocardiographic and echocardiography measurements were recorded.

Pre-treatment and follow-up electrocardiographic and echocardiography measurements were shown in Table 1 and Table 2 accordingly. Biochemical and haematological findings of the patients were shown in Table 3. At the second day of boceprevir treatment, the patient experienced orthostatic hypotension with blood pressure of 70/50 mmHg. After removal of amlodipine, she recovered and her treatment was continued with valsartan 160 mg alone without any hypotensive attack.

Table 1. ECG findings of the patient

	Heart rate (bpm)	QTc (ms)	PR interval (ms)	QRS duration (msn)
Pretreatment	69	437	130	88
First day of lead-in treatment	73	404	132	80
First week of lead-in treatment	68	425	120	90
Pre-boceprevir treatment	71	417	124	90
First day of boceprevir	77	420	138	88
First week of boceprevir	75	431	146	89
Second week of boceprevir	74	425	146	86
Third week of boceprevir	80	420	142	100
First month of boceprevir	84	421	144	90
Second month of boceprevir	81	430	140	92

QTc: corrected QT interval

Table 2. Echocardiography findings of the patient

	Pre-boceprevir treatment	Third day of boceprevir	First week of boceprevir	Second week of boceprevir	Third week of boceprevir
LVEF (%)	66	66	67	67	65
Stroke volume (ml)	82,3	98,8	82,9	90,9	83,3
LVEDD (mm)	46	46	46	46	46
LA diameter (mm)	43	45	48	45	45
Aortic velocity (m/s)	1,20	1,17		1,14	1,20
PASP (mmHg)	24	25		24	24
Pulmonary artery flow velocity (m/s)	1,07	1,10		0,90	1,05
Mitral E/A ratio	0,70	0,69	0,71	0,89	0,83
Left lateral TDI E'/A' ratio	0,57	0,55	0,67	0,54	0,36
Left lateral TDI S wave (cm/s)	10	7	10	10	14
RV diameter (mm)	31	32	33	30	31
Tricuspid E/A	0,74	0,78	0,61	0,55	0,57
Tricuspid lateral annulus E'/A' ratio	0,71	0,77	0,77	0,57	0,64
Tricuspid lateral annulus S wave (cm/sn)	14	15	12	11	12
E/E' ratio	7,5	7,5	7,8	7,7	9

LVEF: Left Ventricle Ejection Fraction, LVEDD: Left Ventricle End Diastolic Diameter, LA: Left Atrium, PASB: Pulmonary Artery Systolic Pressure, RV: Right Ventricle, TDI: Tissue Doppler Imaging

Table 3. Biochemical and haematological test results of the patient

	Pre-treatment	First day of lead-in treatment	First week of lead-in treatment	First week of boceprevir	Third week of boceprevir	First month of boceprevir	Second month of boceprevir
WBC	4.01	1.89	2.25	2.07	2.76	1.26	1.29
Haemoglobin	12.6	11.6	11.7	10,8	10.5	10,3	10.9
Platelet	107	94.2	84.9	102	120	82	88
Creatinin	0.74	0.75		0.71	0.74	0.74	0.82
Triglyceride				113			112
HDL	28			29			29
LDL	65			66			65
AST	61	73	42	24	25	27	22
ALT	54	58	32	13	15	16	20
GGT	170	178	142	79	90		125
TSH	2.6				2.8		2.6
PTZ	14.3	14.8	15.3	14.3	15.6		14.2

ALT: Alanine Aminotransaminase, AST: Aspartate Aminotransferase, LDL: Low Density Lipoprotein, HDL: High Density Lipoprotein, GGT: Gama Glutamyl Transferase, TSH: Thyroid- Stimulating Hormone, PTZ: Prothrombine Time, WBC: White Blood Cell

DISCUSSION

Telaprevir and boceprevir were approved by the U.S. Food and Drug Administration (FDA) in May 2011 in combination with peginterferon alpha and ribavirin for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including cirrhosis, who are treatment-naive or who have been previously treated with interferon-based treatment.[7,8] Both agents inhibit the NS3/4A serine protease which is essential for replication of HCV.9 The introduction of the protease inhibitors or direct-acting antivirals significantly has changed the landscape of HCV management for both treatment naive and treatment-experienced patients. Boceprevir is used in combination with peginterferon and ribavirin to treat chronic HCV.[10]

Amlodipine usage especially in combination with angiotensin receptor or angiotensinogen converting enzyme blocker has been very popular for the treatment of systemic hypertension.[11,12] But its use in clinical practice also brings out rare drug-drug interactions such as statin, macrolids and telapravir.[3,13] Although interaction of boceprevir with calcium channel blockers explained as a class effect was reported in the literature, its interaction with amlodipine was not addressed individually. Here we reported a case with hypertension whose blood pressures were under control with fixed-dose combination of valsartan and amlodipine. Two days later after starting boceprevir, hypotension was developed. The possible explanation of this situation is inhibition of CYP3A4 enzyme system by boceprevir, and indirectly increases of amlodipine concentration in blood circulation.

Long-term effects of boceprevir on cardiovascular system haven't been known. The literature usually gives examples of drug-drug interactions of boceprevir with other concomitantly used medications such as statin, amiodarone, sildenafil.[14] To enlighten this aspect, here we followed the patient electrocardigraphically and echocardiographically for two months after starting boceprevir treatment. Both electrocardiography and echocardiography results revealed similar findings. The related parameters didn't change significantly at follow-up.

In conclusion, we found that combination of amlodipin and boceprevir resulted in drug-drug interaction via cytochrome P450 pathway and led to severe hypotension. But we didn't find any adverse effect of boceprevir on heart in two-month follow-up by using electrocardiography and echocardiography. Further studies are needed to clarify long-term cardiac effects.

Abbrevations

TDI: Tissue Doppler İmaging, **LVEF:** Left Ventricle Ejection Fraction, **LVEDD:** Left Ventricle End Diastolic Diameter, **LA:** Left Atrium, **PASB:** Pulmonary Artery Systolic Pressure, **RV:** Right Ventricle, **QTc:** Corrected QT Interval, **ALT:** Alanine Aminotransaminase, **AST:** Aspartate Aminotransferase, **LDL:** Low Density Lipoprotein, **HDL:** High Density Lipoprotein, **GGT:** Gama Glutamyl Transferase, **TSH:** Thyroid-Stimulating Hormone, **PTZ:** Prothrombine Time, **WBC:** White Blood Cell

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