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Olgu sunumu/ Case report

Asymptomatic Transaminase Elevation Due to Bupropion: Case Report and Overview of the Literature

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ABSTRACT

Generally bupropion is considered as a safe and well-tolerated antidepressant for the treatment of major depression. In preclinical studies, mild and transient elevation of serum aminotransferases was observed and also phase 3 studies revealed this increase as up to 1%. In this case report, we aimed to present a major depression patient with asymptomatic elevation of liver enzymes after bupropion treatment which returned to normal values after bupropion stopped.

Keywords: Bupropion, side effect, transaminases,

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Bupropion Kullanımına Bağlı Asemptomatik Transaminaz Yükselmesi:

Olgu Sunumu ve Literatür Taraması

ÖZET

Bupropion major depresyon tedavisinde genel olarak güvenli ve iyi tolere edilebilir bir seçenektir. Preklinik çalışmalarda serum transaminaz seviyelerinde hafif ve geçici yükselmelere neden olduğu gösterilmiştir. Bu vaka sunumunda başka bir rahatsızlığı olmayan major depresyon hastasında bupropion kullanımından sonra gelişen ve ilaç kesilince düzelen transaminaz yükselmesi rapor edilmektedir.

Anahtar sözcükler: Bupropion, yan etki, transaminazlar,

INTRODUCTION

Generally bupropion is considered as a safe and well-tolerated antidepressant for the treatment of major depression. It inhibits reuptake of noradrenaline (NE) and dopamine (DA) in neurons as it's primary mechanism of action (1). In a study evaluating bupropion extended release (XR); dry mouth, flatulence, constipation and nausea have found to be the most frequently seen side effects but none of them were significantly different when compared with placebo. In preclinical studies, mild and transient elevation of serum aminotransferases was observed and also clinical studies revealed this increase as up to 1% (2, 3).

In this case report, we aimed to present a major depression patient with asymptomatic elevation of liver enzymes after bupropion treatment which returned to normal values after bupropion stopped.

CASE

An otherwise healthy 32 years old man admitted to our clinic with complaints of depressive symptoms. He has been treated with first fluvoxamine and then mirtazapine without any improvement for 6 months. For the last 2 months he stopped his medication and his medication was started again with bupropion 150 mg/day. Before treatment, his laboratory test results including serum aminotransferases were within normal limits. Bupropion dosage increased to 300 mg/day after one month due to lack of response. His symptoms did not improve one month later therefore laboratory tests including complete blood count, liver and kidney functions, electrolytes, vitamine B12 and thyroid functions tests were repeated. All of the results were normal except alanine-aminotransferase (ALT) which was 146 U/L (greater than 3 times the upper limit of normal). He denied alcohol consumption and any other drug usage. He was referred to gastroenterology department. Total protein, albumine, globuline, urea, creatinine, total bilirubine, glucose, ferritine, transferrine,

ceruloplasmin, and serum electrolytes were all normal; erythrocyte sedimentation rate (ESR) was 5 mm/hr, c-reactive protein (CRP) was 3.36 mg/dL and total cholesterole was 17 mmol/L. Serology for hepatitis A, hepatitis B, hepatitis C, human immun deficiency virus, rubella, cytomegalovirus, toxoplasma, herpes simplex virus type 1-2 and Ebstein-Barr virus were negative. His coagulation parameters (APTT, PT INR, PT S) were normal and abdominal ultrasound scan showed no pathology. Elevation of the ALT was attributed to the bupropion treatment and bupropion stopped. After cessation of bupropion ALT decerased to 72 U/L within a week which then returned to normal values after one month. His treatment continued with milnacipran 50 mg/day and his depressive symptoms responded to this treatment.

DISCUSSION

Transient elevation of transaminases and hepatotoxicity can be seen due to all antidepressants albeit scarce. There is insufficient data on the frequency of Drug Induced Liver Injury (DILI) for most of the antidepressants. In a recent review, MAO inhibitors, tricyclic/tetracyclic antidepressants, nefazodone, bupropion, duloxetine, and agomelatine were reported to cause DILI. Citalopram, escitalopram, paroxetine, and fluvoxamine were reported to be safer. Up to now, bupropion induced liver injury were reported in 6 cases. One of them was similar with our case with respect to asymptomatic liver enzymes elevation (4). In 4 of the cases, cessation of the bupropion caused resolution (2, 4, 6, 7) and 2 of them ended with death (5, 8). In almost all cases there were comorbid diseases which can cause liver enzyme elevation and multiple drug usage. Detailed information about these cases are shown in **Table 1**.

Table 1. Overview of the characteristics of bupropion induced liver injury cases.

	Age/Gender	Concurrent Diseases	Other medications	Dosage	Symptoms	Onset of symptoms
Oslin 1993[8]	73 female	Hypothroidism Seronegative arthirits Gastritis Adult onset DM Heart block Conjestive heart failure	Thyroxine 0.1 mg/d Transdermal nitrolycerin 0.4mg/hour Lithium carbonate 300 mg/d Prednisone 5mg/day	400 mg/d	Asymptomatic	54 days
Alvaro 2001[4]	49 female	Hypertension Alcohol < 20 g/d	Nebivolol 5 mg/day	300 mg/d	Asthenia Nausea Jaundice Acholic stool Hyperchromic urine	20 days
Khoo 2003[9]	41 male	Hyperthyroidism	Carbimazole 15 mg/d Propranolol 10 mg/d Alcohol (1–2 glasses of beer/wk) Acetaminophen two weeks prior to admission 0.5–1 g for up to 2 days	150 mg/d	Jaundice Nausea Dyspepsia Lethargy Epigastric discomfort	10 weeks after cessation
Bagshaw 2003[10]	24 male	-	-	300 mg/d	İntermittent fever Generalized maculopapular rash	21 days
Hu 2000[11]	41 male	Chronic Hepatitis C	-	200 mg/d	Subjective fever Chills Malaise Muscle aches Anorexia nausea	41 days
Humayun 2007[12]	55 male	Hypertension Hyperlipidemia Prosthetic mitral valve	Warfarin Paroxetine Metoprolol XL Atorvastatin Aspirin	300 mg/d	Hematuria Easy bruising Jaundice Fevers Nausea Vomiting Fatigue	6 months

Triple times elevation of ALT or double times elevation of ALP from upper limit of normal range suggests DILI (9). In our patient, all possible causes of elevation of liver enzymes were examined and no apparent cause were found. Because of normal levels before bupropion treatment and returning to normal levels after drug cessation highly suggests DILI. Liver injury has classifed as hepatocelullar, cholestatic and mixed types (9). Both hepatocellular and cholestatic type DILI were reported due to bupropion before. Our patient's liver injury was hepatocellular type because ALT was elevated and ALP was normal. In conclusion, drug induced hepatotoxicity is idiosyncratic, acute and hard to predict. Early diagnosis and intervention is crucial. Elevation of liver enzymes may not be sensitive but it is definitely warning.

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