

A RARE CASE OF TIBOLONE INDUCED TOXIC HEPATITIS

Erkan Cüre MD¹, Kasım Demir MD¹, Cem Koçkar Assoc. Prof. MD², Abdülkadir Baştürk MD¹, Altuğ Şenol MD²

¹ Suleyman Demirel University, Medical Faculty, Department of Internal Medicine, Isparta, TURKEY

² Suleyman Demirel University, Medical Faculty, Department of Gastroenterology, Isparta, TURKEY

ABSTRACT

Tibolone is a synthetic steroid with estrogenic, androgenic and progestogenic properties used primarily for the treatment of menopausal symptoms. Tibolone may rarely cause hepatotoxicity. Here, we report tibolone induced hepatotoxicity.

A 52 year-old woman was admitted to our hospital with a complaint of abdominal pain. Her hepatic function tests were found to be elevated. Impairment of liver function

tests was thought to be caused by using tibolone, and tibolone was stopped. During follow up, her liver function tests were normalized in fifteen months.

It is known that drug induced hepatotoxicity is usually normalized in 3 months to 1 year. But it should be kept in mind that normalization of hepatotoxicity may rarely prolong to more than one year as in this case.

• **Key Words:** Tibolone, hepatotoxicity, toxic hepatitis. *Nobel Med* 2008; 4(2): 33-35

ÖZET

TİBOLON KULLANIMINA BAĞLI GELİŞEN NADİR BİR TOKSİK HEPATİT VAKASI

Tibolon postmenopozal semptomların tedavisinde kullanılan, östrojenik, androjenik ve progestojenik özellikleri olan sentetik bir steroiddir. Tibolon nadiren hepatotoksositeye yol açar. Tibolon kullanımına bağlı hepatotoksosite gelişen bir vakayı sunuyoruz.

Elli iki yaşında kadın hasta karaciğer fonksiyon test-

lerinde yükselme olması nedeni ile hastanemize başvurdu. Karaciğer fonksiyon testlerindeki bozukluğun tibolona bağlı olduğu düşünüldü ve tibolon kesildi. Takiplerinde, hastanın karaciğer fonksiyon testleri 1,5 yıl içinde normale döndü. İlaça bağlı hepatotoksitenin genellikle 3 ay ile 1 yıl arasında düzeldiği bilinmektedir. Ancak bizim vakamızda olduğu gibi hepatotoksitenin düzelmesinin 1,5 yıla kadar uzayabileceği de akılda tutulmalıdır.

• **Anahtar Kelimeler:** Tibolon, hepatotoksosite, toksik hepatit. *Nobel Med* 2008; 4(2): 33-35

INTRODUCTION

Most known causes of hepatotoxicity are drugs. It is known that drugs can damage liver ranging from asymptomatic hepatic enzyme abnormality to hepatic failure. Main treatment of toxic hepatitis is to stop causing agent. Although prognosis can be variable, hepatic enzymes normalized in a short time after the causing agent stopped.

The impression has arisen that tibolone, usually prescribed as a second-line hormone therapy product in widespread, is prescribed to women with a clinical background different than that of women prescribed combined estrogen + progestogen therapy.¹ We present a case with toxic hepatitis causing by tibolone.

CASE REPORT

A 52 years old women patient has admitted to another hospital because of epigastric pain. Her hepatic function tests were found to be elevated. From her history we learned that she had used tibolone for 5.5 years and last year, as a 2-3 fold elevation in her liver function tests was detected she has stopped tibolone. Physical examination revealed that blood pressure 120/70 mmHg, pulse rate 76 per minute, and axillary temperature 36.5°C. Hepatosplenomegaly was not found and remainder of examination was also normal. In laboratory results Aspartate aminotransferase (AST) was 65 U/L (0-37), alanine aminotransferase (ALT) was 77 U/L (0-41). Alkaline phosphates (ALP), gamma-glutamyltransferase (GGT), bilirubin and albumin were normal. HBsAg, anti-HBs, anti-HCV, anti-HAV IgM, Cytomegalovirus IgM, and Epstein-Barr virus IgM were examined for acute hepatitis, and found negative. We thought elevation of liver function tests was due to tibolone treatment. Control examination 1.5 months later, revealed that AST 102, and ALT 226 U/L. Liver was normal in ultrasonography. Differential diagnosis included autoimmune hepatitis, primary biliary cirrhosis, alpha1 antitrypsin deficiency, Wilson's disease, and hemochromatosis, antinuclear antibodies, antimitochondrial antibodies, anti-liver kidney microsomal type 1 antibody, smooth muscle antibodies were examined and found negative and alpha1 antitrypsin, ceruloplasmin, copper levels in serum and urine, and ferritin were examined and found normal. As elevation of liver function tests was present for more than 6 months and etiology of elevation was not determined, liver biopsy was performed. Biopsy showed nonspecific differences. Laboratory tests repeated. Consequently, ALP 631 U/ml (0-270), GGT 322 U/ml (5-61), total protein 8.1 g/dl, albumin 5.0 g/dl, total bilirubin 0.83 mg/dL were found. Endoscopic retrograde cholangiopancreatography (ERCP) was performed to investigate primary biliary

cirrhosis and sclerosing cholangitis. Choledochocyst was detected in ERCP. Abdomen tomography was performed and free opaque fluid was detected in Morison pouch, around duodenum, in retroperitoneal space, near left liver lob, and between liver and stomach. Also duodenal wall thickness was detected with tomography. Oral feeding was stopped and suitable antibiotic therapy was administered. Two days later, minimal free fluid was detected in perihepatic and pelvic space with ultrasonography. Diffuse sensitivity of abdomen was present in physical examination. As perforation suspected abdominal surgery was performed. Perforation was not detected but liver biopsy was taken. Examination of biopsy material showed acute cholangitis, thickness in liver capsule, and acute inflammation in serosal surface of liver. After administration of suitable antibiotic therapy and ursodeoxycholic acid 3 times a day, her liver function tests were decreased to value of 70-80 U/L in two weeks and GGT, ALP values were normalized. As the patient got better clinically and radiologically, we discharged her from the hospital. She came to polyclinic control every month because of toxic hepatitis. AST and ALT values were normalized 1.5 years later from stopping tibolone.

DISCUSSION

Drug induced hepatotoxicity is seen frequently in gastroenterology clinics. No specific treatment for drug induced hepatotoxicity exists. It was reported that drug induced hepatotoxicity is usually normalized in 3 months to 1 year.^{2,3} In this case liver function tests were normalized 1.5 years later from discontinuing of tibolone treatment.

Several mechanisms are supposed to induce hepatopathy: inhibition of the β -oxidation⁴ and oxidative phosphorylation⁵, inhibition of gluconeogenesis⁶ and urea synthesis⁷, a steatogenic effect⁸, and a decrease of intracellular carnitine.^{9,10}

The diagnosis of drug induced hepatotoxicity is usually based on exclusion of other possible causes of hepatic dysfunction and on the temporal association between drug administration and the onset of liver disease while liver biopsy may allow a correct diagnosis.^{11,12} Several scales were described to diagnose toxic hepatitis. Performance, objectivity, and quantitativity of CIOMS scale are better than others.^{2,3} We diagnosed toxic hepatitis in this case by CIOMS scale.

Tibolone [(7 α ,17 α)-17-hydroxy-7-methyl-19-norpregn-5 (10) en-20yn-3-one] is a synthetic steroid with estrogenic, androgenic and progestogenic properties used primarily for the treatment of menopausal symptoms.^{13,14} Tibolone will suppress endogenous estrogen →

secretion and follicular maturation by suppression of LH and FSH secretion and has a protective influence for potential osteoporosis that may contribute to its therapeutic efficiency.¹⁵ A case with tibolone induced hepatotoxicity has been reported formerly.¹⁶

Our case has been using tibolone for 5.5 years. When she admitted to the hospital, elevation of AST and ALT was detected. Tibolone treatment was stopped and patient followed as an out-patient. After discontinuing of tibolone liver function tests were not normalized and investigations could not explain the etiology. Liver biopsy was performed and no histopathological finding was detected. Acute cholangitis was detected and was treated. Although acute cholangitis was treated, 2-3 times elevation of liver function tests persisted. Elevation of AST and ALT before acute cholangitis and persistence of elevated liver function tests after cholangitis support that hepatotoxicity was caused by tibolone treatment. Coledoco cyst is a rare pathology in our country. It is

usually presented with jaundice. In our patient coledoco cyst was very small and GGT and ALP were not elevated. So we did not think coledoco cyst caused to elevation of liver function tests. We thought tibolone induced hepatotoxicity and liver function tests were normalized 1.5 years later from discontinuing of tibolone treatment.

CONCLUSION

Drug induced hepatotoxicity is seen frequently in gastroenterology clinics. When hepatotoxicity is detected, the agent which is responsible for this condition must be discontinued. Hepatotoxicity usually improves immediately in months after discontinuing of drug. Rarely, hepatotoxicity could persist for a long time. Moreover like present case hepatotoxicity could persist more than 1 year. It should be remembered that tibolone may cause hepatotoxicity, and liver function tests should be controlled with a certain periods during the treatment with tibolone.



C	CORRESPONDING AUTHOR: Erkan Güre MD, Suleyman Demirel University, Medical Faculty, Department of Internal Medicine, Isparta/TURKEY erkancure@yahoo.com
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