Propylthiouracil Hepatotoxicity Seen with Jaundice and its Treatment by Steroids

Propiltiourasil Kullanımına Bağlı Hepatotoksik Sarılık ve Steroidle Tedavisi

Propiltiourasil Sarılık / Propylthiouracil Jaundice

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Özet

Propylthiourasil (PTU) hipertiroidi tedavisinde yaygın olarak kullanılmaktadır. PTU' in hepatotoksik etkisi oldukça nadirdir ve mekanizması bilinmemektedir. Hepatotoksik etkisi sıklıkla subklinik olmakla birlikte nadiren karaciğer nekrozuna da yol açabilmektedir. Olguların çoğunda PTU' nun kesilmesinden sonra karaciğerin tamamen iyileşmesine rağmen, ender olarak ilacın kesilmesine rağmen karaciğer nekrozuna da neden olabilir.

Anahtar Kelimeler

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Abstract

Propylthiouracil (PTU) is widely used in the treatment of hyperthyroidism and rarely leads to hepatotoxicity by an unknown mechanism. The hepatic damage caused by propylthiouracil is generally subclinical, but very rarely, it may be associated with severe liver injury and submassive hepatic necrosis. Although discontinuing of the drug result in full recovery in most cases, hyperbilirubinemia and liver damage may increasingly continue in spite of discontinuation of the drug.

Keywords

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Introduction

Propylthiouracil (PTU) is widely used in the treatment of hyperthyroidism. Hepatotoxicity is seen 0.2-0.3 % at the patients using thionamides, but actually the real incidence is unknown. Hepatic damage seen in patients that use PTU is the mixed type in which both cytotoxic and cholestatic pattern seen together with elevated transaminase values. The pathogenesis of PTU hepatotoxicity is unclear, but it's thought to be an allergic response to the host [1]. The hepatic damage caused by PTU is generally subclinical. Very rarely PTU therapy may be associated with severe liver injury and submassive hepatic necrosis. But, in most cases, discontinuing of the drug result in full recovery [2]. However, in spite of discontinuation of the drug, hyperbilirubinemia and liver damage may continue to escalate. In this case, treatment options and type of treatment is a controversial issue.

We reported a treatment with steroids and radioactive iodine (RAI) for a case of Graves' disease in a young female patient with progressively increased bilirubin levels from PTU, even after discontinuation of the drug.

Case Report

An 18-year-old female patient with the complaints of palpitations, fatigue, insomnia, nervousness, tremor in hands, was diagnosed with Graves' disease after a work up 1.5 years ago and was put on PTU 300 mg/day, propranolol 50 mg/day. The liver function tests were normal, no jaundice and hepatitis episodes were seen and no alcohol or drug usage before the initiation of the drug therapy. At routine checks; AST: 186 IU/ml (10-37), ALT: 414 IU/ml (0-45), ALP: 218 IU/ml (30-120), GGT: 110 IU/ml (10-60), total bilirubin: 2 mg/dl, direct bilirubin: 1.3 mg/dl was determined so drug was stopped. But, after 1 month, due to the recurrence of hyperthyroidism high-dose propylthiouracil (300 mg/day) treatment was started again (in another hospital). The patient had a history in the next 6 months to start and stop PTU for a few more times in the same way. When referred to our clinic with mild jaundice, AST: 623 IU/ml, ALT: 942 IU/ml, GGT: 69 IU/ml, albumin: 4.4 mg/dl total bilirubin 5.6 mg/dl, direct bilirubin: 4.75 mg/dl, prothrombin time (PT): 14 sec. were determined and she was admitted to the service. At the physical examination during the time of admission; Pulse: 70/min, blood pressure: 100/60 mm/Hg were determined. The patient's skin was significantly icteric but there was no Graves ophthalmopathy and skin lesions. Both lobes of the thyroid were diffusely enlarged. Liver and spleen were not palpable. Not continued medication during hospitalization, in spite of falling transaminases rather total / direct bilirubin levels remained high (AST: 84 IU/ml, ALT: 195 IU/ml, GGT: 30 IU/ml, albumin: 4.2 mg/dL, total bilirubin: 14.6 mg/dL, direct bilirubin: 8.2 mg/dl). At the thyroid function tests (as result of the influence of PTU), TSH: 0.14 IU/ml (0.34-4.2) (FT3: 3.72 pg/ml (2.5-3.9), FT4: 1.36 ng/dl(0.7-1.4), Anti-TPO (+), anti-TG: (+). Thyorid hormone receptor antibody (TRab) colud not be performed because of financial reasons. Ultrasonography revealed a diffusely swollen thyroid with low echogenicity, thyroid blood flow inceased and nodule was not observed The repeated hepatitis virus serologies (HBsAg, hepatitis B infection, HbeAg, antiHBc IgM, anti-HCV) were observed negative. Autoimmune hepatitis antibodies (ANA, AntidsDNA, AMA, LKM-1, Anti-SSA, anti SSB, Sm-antibody, ANCA, AntiJo, AntiSCL 70, Anti SM/RNP) were seen as negative. No pathology was observed at the repeated abdominal ultrasound imaging. With absolute resting AST/ALT levels didn't rise over twice, but on the 23rd day of follow-up total/direct bilirubin rose up to 26.0/12.7 mg/dl and GGT:42 IU/ml. During the hospitalization period, thyrotoxic situation of the patient is increased, surgical treatment was considered but given up as the surgery under anesthesia seemed to be risky. After these values, methyl prednisolone 60 mg/day treatment was started. On the next day after the initiation of steroid was observed that total bilirubin and direct bilirubin were 25.7 mg/dl and 12.7 mg/dl, respectively. RAI treatment (high-dose 18 milliCurie) was performed to the patient after the second day of treatment with steroid therapy. In the following days, progressive improvement was seen in bilirubin levels and thyroid function tests. Steroid therapy was continued with tapering gradually in 3 months. Treatment with radioactive iodine maintained euthyroid state at the follow-up of patient. During follow-up within 1 year after the cessation of steroid therapy, all values were normal (Table 1).

Table 1. Patient's biochemical values

	Before PTU	After PTU	She was admitted to the service	Next values	After methyl-prednisolone and RAI	After 3 months	After 1 year
AST IU/ml (10-37)	32	186	623	84	39	38	34
ALT IU/ml (0-45)	40	414	942	195	44	42	31
GGT IU/ml (10-60)	56	110	69	30	54	28	36
T.Bil mg/dl (0,3-1,2)	0.9	2	5.6	14.6-25.7	1.0	1	1,1
D.Bil. (0-0,2)	0.1	1.3	4.75	8.2-12.7	0.1	0,14	0,16

Discussion

Graves' disease (GD) is an autoimmune disorder in which antibodies activate the thyrotropin receptor (TSHR) causing a hyperfunction of the thyroid gland. This activation stimulates follicular hypertrophy and hyperplasia, leading to thyroid enlargement and increases thyroid hormone production. The three treatment modalities for Graves' hyperthyroidism include the use of thionamides (antithyroid drugs: PTU, methimazol (MMI) and carbimazole), radioactive iodine (RAI) therapy or surgery. Patients in Australia, the UK and Europe are more likely than their North American counterparts to receive an initial course of thionamide therapy prior to the consideration of RAI. Surgery has the highest long-term remission rate (95%) but is not without risks [3].

PTU has been used widely in the treatment of hyperthyroidism. During the use of PTU, skin reactions, agranulocytosis, arthralgia, hepatotoxicity, vasculitis, sialadenitis, hypoglycemia, pancreatitis can be seen as the undesired side effects PTU is a derivative of thiourea, may cause hepatic damage and rarely cholestasis. Although the pathogenesis is unclear, hepatotoxicity of PTU is thought to be responsible for the allergic response in the host [1]. PTU-induced hepatotoxicity is usually seen in the first 90 days after treatment has begun, but cases of hepatotoxicity have been reported, even after 1 year of treatment initiation [4]. In our patient, the first of toxicity was seen 1 year

after the initiation of drug therapy and improved after discontinuation of the drug. Once again, the development of toxicity after restarting the drug therapy, supports the drug-induced toxicity. Therefore, these patients should be monitored closely for hepatotoxicity. Hyperthyroidism itself can cause liver dysfunction and mild enzyme elevation, jaundice is much less common finding [5]. The height of bilirubin seen in our case, is contributed to hyperthyroidy, however, 2 times transaminase, ALP, GGT elevation seen under treatment with PTU, the recovery of findings after the treatment is stopped in the first reaction and determination of biochemical parameters compatible with mixed type hepatic damage supports that the elevation of serum bilirubin was induced by PTU. In this case, immediate PTU treatment discontinuation is needed. In our case patient was using 300 mg PTU and treatment was cut off. In the majority of cases, the support treatment seems to be useful, but secondary complications of liver failure deaths can be seen up to 25%. Therefore, early detection of fulminant hepatitis has great importance (<11 years and> 40 years of age), jaundice lasts more than 7 days, prolonged prothrombin time, encephalopathy, bilirubin level is high [6]. PTU- induced liver damage biopsy specimens with intracanalicular cholestasis and mild periportal inflammation were seen, but hepatocellular architecture preserved in general [5]. Our patients scheduled for liver biopsy to determine the extent of the damage, but operation failed as the patient refused.

Hanson recommended the following practical criteria for the diagnosis of hepatitis caused by the use of drugs; 1-clinical and laboratory evidence of hepatocellular injury, 2-symptoms begin to be associated with drug therapy time, 3- serological evidence of HAV, HBV, CMV or EBV infection, 4- absence of conditions that can cause acute hepatic damage such as shock and sepsis, 5- absence of chronic liver damage findings, 6-particularly the absence of other drugs used for the treatment known as hepatotoxins [7].

In our case, there was no history about drug use, transfusion of blood or blood products. Our patient did not have a clinic application suggestive of liver disease, there was no situation that can cause acute hepatic damage as well. Clinical and laboratory findings of hepatocellular injury were present. In addition, anti-HCV and HCV-RNA were negative. No history of alcohol abuse or alcoholic liver disease was present. Serological studies of viral etiology were excluded. However, drug treatment was associated with a temporary onset of symptoms. Also there was no use of any medication known as hepatotoxic. All these findings seem to be consistent with the criteria imposed by Hanson for the diagnosis of hepatitis caused by drugs [7].

As no specific treatment was given for hyperthyroidism prominence of thyrotoxicosis was seen. Surgical treatment was seen as risky because of the thyrotoxicosis and severe hyperbilirubinemia. There is very limited data available on the use of steroid therapy for PTU-induced liver injury.

However, at the cases reported by Ichiki and colleagues; 21-year-old graves' disease cases, serious hyperbilirubinemia developed after PTU (Total bilirubin: 23.3 mg/dl, direct bilirubin: 16.3 mg/dl) and severe liver injury (AST: 593 IU/ml, ALT: 502 IU/ml) developed patients were given 3 days 500 mg methyl prednisolone and had continued with prednisolone 30 mg orally after. Liver function tests gradually improved after treatment and got back to normal in about 1.5 months. The first treatment to be given in case of PTU hepatotoxicity is I 131 therapy. Other alternative therapies are ipodate sodium, iopanoic acid, ate, lithium carbonate, plasmapheresis, and dialysis [8].

In our case, after exclusion of all other causes, 60 mg intravenous methyl prednisolone treatment was started. Increase in the level of bilirubin in the first days after treatment stopped the inspections of 1 mg/dl decrease in the level was observed. The following day the patient was prescribed RAI therapy. Rapid and progressive improvement in bilirubin levels were seen in the patient's follow-up. At the same time improvement at the toxic statement was observed. Steroid dose was reduced gradually and patient was discharged from hospital.

As a result, we think that the patients started PTU due to the hyperthyroidism should be followed carefully and strictly for hepatotoxicity, jaundice. Also we think that, the steroid therapy is a good alternative for the severe bilirubin level rise and jaundice caused by PTU after the exclusion of all other the reasons.

Competing interests

The authors declare that they have no competing interests.

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