

Relationship of recovered hepatitis B infection with appearance of toxic propylthiouracil hepatitis

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ABSTRACT

Aim To investigate the relationship between recovered hepatitis B infection with appearance of toxic propylthiouracil (PTU) hepatitis and point out the growing importance of the use of drugs in the development of hepatitis.

Methods A case of a 45-year-old female patient with suspicion of acute viral hepatitis who had polypragmasy of drugs in the last ten years, due to the polymorphism of symptoms/illnesses (diabetes mellitus, depression, hypertension, hypothyroidism) was presented.

Results A female patient had hyperthyroidism after resolved viral hepatitis B with HBsAg seroconversion (HBsAg negative, anti-HBs positive). PTU had the greatest potential for hepatotoxicity of all administered drugs. After corticosteroid therapy there was a significant improvement in liver function tests. In the course of the disease there was no change of hepatitis markers and exacerbations of hepatitis B.

Conclusion Clinical practice should comprehensively monitor the effects of the intricate and tight connection between drugs, liver and endocrine system in order to better resolve all manifestations, complications and worsening of one or another organic system.

Key words: drugs, hepatotoxicity, hyperthyroidism, HBsAg seroconversion

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INTRODUCTION

Toxic liver damages cause about 5 % of all jaundice and about 25 % massive necrosis of the liver. Drugs are becoming an increasingly important cause of jaundice and massive necrosis of the liver which should be given special attention when taking history of icteric patients (1,2). Hepatotoxic agents may be either real hepatotoxicants or leading to liver damage with idiosyncrasy. Idiosyncratic liver injury is unpredictable, it occurs only in susceptible individuals and independent of the drug dose. The incidence of the liver damage is 19/100.000 of treated people, women become ill more often and mortality rate is higher than 10 % (3).

Propylthiouracil (PTU, 6-n-propylthiouracil) is a drug derived from thiouracil that was used for the treatment of hyperthyroidism (including Grave's disease). It works by reducing the amount of thyroid hormone produced by the thyroid gland. Side effects are not common and occur in 1-5% of patients. The most common reactions are: rash on the skin, itching, arthralgia, fever and nausea. It can also develop transient neutropenia, and very rarely agranulocytosis, vasculitis, lupus-like syndrome and acute or chronic interstitial nephritis (4). In 2009 the US Food and Drug Administration (FDA), after an evaluation of 34 cases of serious damage to liver function in adults and children, some of whom had a fatal outcome, published a warning about the risk of serious liver damage in the use of propylthiouracil (5). The European Medicines Agency (EMA), on the basis of security information and new FDA recommendations, made a decision on the need for revision of a summary of product characteristics and instructions for patients. The consequence is that the propylthiouracil is no longer recommended as a drug of first choice. The PTU is still the treatment of choice in patients where it is necessary to apply antithyroid medications, only during and immediately before the first trimester of pregnancy, as it is associated with less teratogenic effects (changes in the soft part of the scalp) than methimazole (6,7). Cochrane systematic review has not found even one randomized study which provides evidence to women and their doctors about the most effective drugs against overactive thyroid gland, which also have the lowest risk of harmfulness (7).

Hepatic dysfunction in patients with hyperthyroidism may be a consequence of the disease or the

side effects of therapy (8). Also, there are many data which suggest that antithyroid drugs with thyreosuppressive effect can have immunomodulating effects and cause ANCA (Antineutrophil cytoplasmic antibodies/ANCAs) seropositive vasculitis, myasthenia gravis, Graves' disease, other autoimmune diseases and some immunosuppressive effects (9-11). The PTU modifies the function of natural killer cells (NK cells) and B and T lymphocytes (12).

The aim of this paper was to investigate the relationship between PTU toxic hepatitis and viral hepatitis B in the patient with suspicion of acute viral hepatitis infection who had polypragmasy of drugs in the last ten years due to the polymorphism of symptoms/illnesses (diabetes mellitus, depression, hypertension, hypothyroidism) and to point out the growing importance of the use of drugs in the development of hepatitis.

PATIENT AND METHODS

Patient and study design

A 45-year old female patient was admitted to the Department of Infectious Diseases at the Cantonal Hospital of Zenica, Bosnia and Herzegovina during July 2015 with suspicion of acute viral hepatitis infection.

The disease started seven days before hospitalization with mild abdominal pain, daily vomiting, loss of appetite, general weakness, joint pains, swelling of the left ankle joint, non-specific rash on the skin. Just before the reception she noticed dark urine and eyes and skin yellowing.

Since 2003 she had been treated with 20 mg paroxetine (half + 0 + half), alprazolam 1 mg (1+0+0) and risperidone 1 mg (0+0+1) tablets for depression. Because of diabetes mellitus she was treated with 500 mg metformin (3x1) tablets. Because of hypertension, she was treated (several years) with 5 mg lisinopril (2x1) tablets. In 2012, hepatitis B markers were done accidentally: negative HBsAg, positive anti-HBs and anti-HBc, and negative anti-HCV. She denied hepatitis B virus infection or having anyone in the family who suffered from hepatitis B. In 2008 hyperthyroidism was diagnosed with one non-growing warm node in the left lobe, and she denied surgery. In the beginning of hyperthyroidism she was treated with thiamazole (1x5 mg).

During 2010 the hormonal status was normal and hormonal therapy was terminated. In early 2014, she had again symptoms of hyperthyroidism, hormonal status was back to hyperthyroidism values and thiamazole 1x10 mg was administered. Six months later, for unknown reasons, therapy was changed into PTU (propylthiouracil) 50 mg (3x½), and later in during the course of the disease propylthiouracil 3x50 mg plus propranolol 40 mg (2x½). In February 2015, 20 mCi I-131 (radioactive iodine) was administered, and later PTU 50 mg 3x½ initially, and then 2x½. She denied earlier allergies to food and medications. In the family history, her sister suffered from multiple sclerosis (early stage of the disease).

At the time of the admission, the patient was middle developed, well-fed, 76 kg, afebrile, conscious, with icteric skin and sclera, eupneic, giving the impression of the patient of medium gravity. Physical findings of the heart and lung were normal, blood pressure was 130/80. The abdomen was soft, sensitive in epigastrium and in right upper quadrant. Liver and spleen were palpable for about 2 and 1 cm, respectively; liver was hard, with a sharp edge. There were pain and swelling on the left ankle joint.

Methods

Laboratory analyses of the blood were performed at the Department of Laboratory Diagnostics in Cantonal Hospital Zenica (Vitros 350, Ortho Clinical Diagnostics, Raritan, NJ, USA) 1st, 2nd, 7th, 14th, 21st and 28th day of hospitalization as follows (Table 1): serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), gamma glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), thyroid stimulating hormone (TSH), free triiodothyronine (FT3), thyroxine (FT4). The level of copper (12.6-24.3 µmol/L), alpha-fetoprotein (<7.2 IU/mL), and fibrinogen (1.8-3.5 g/L) were determined as well.

Hepatitis A, B and C serologic tests were done at the Department of Transfusion Medicine of the Cantonal Hospital Zenica (Architect i2000SR PLUS, Abbot Diagnostics, Wiesbaden, Germany) included: anti-HAV IgM (<0.8 negative, >1.2 positive), anti HAV IgG (<1 negative, >1 positive),

HBsAg (<0.85 negative, >1 positive), anti-HBs (normal/N <10), anti-HBc (<1 negative, >1 positive), anti-HBc IgM (<1 negative, >1 positive), HBeAg (<1 negative, >1 positive), anti-Hbe <1 negative, >1 positive), anti-HCV (<0.80 negative, >1 positive). PCR (N<20 IU/mL) was done at the University Clinical Center Sarajevo (Real time PCR, Abbot, Wiesbaden, Germany).

Immunological analyses included: DAT (direct antiglobulin test, poly AHG Anti-human globulin) (positive or negative), SCR (red cell screening) on the irregular red cell antibodies I and II (Bio-Rad, California, USA); ANA (antinuclear antibodies), AMA (antimitochondrial antibodies), ASMA (antismooth muscle antibodies), anti-dsDNA (anti-double stranded DNA) (Indirect Immunofluorescence, Euroimmun, Luebeck, Germany), anti LKM-1 (liver kidney microsomal type 1 antibodies), anti LC-1 (liver cytosol antibody), SLA/LP (soluble-liver-antigen/liver-pancreas), M2-3E (BPO) (autoantibodies to mitochondrial antigen-pyruvate dehydrogenase complex (M2), branched-chain 2-oxo-acid dehydrogenase complex and 2-oxo glutarate dehydrogenase complex (3E-BPO), PML (promyelocytic leukemia protein), Sp100 (speckled protein (100 kDa)), gp210 (glycoprotein 210 kDa) (Euroline Profile, Euroimmun, Luebeck, Germany), immunoglobulins IgG (7-16 g/L), IgA (0.7-4.0 g/L), IgM (0.4-2.3 g/L), and IgE 167 (<100 IU/mL) (BN System, Siemens, Erlangen, Germany).

Ultrasound of the abdomen (SA-8000, Medison Co., Seoul, Korea) was done at the admission, as well as ophthalmologist examination.

RESULTS

Immediately on admission the basic laboratory findings were done, which are shown in Table 1 according to the days of hospitalization.

The results of hepatitis A, B and C markers were: HBsAg-negative, anti-HBs positive >1000, anti-HBc positive, anti-HBc IgM negative, HBeAg negative, anti-HBe positive, anti-HCV negative, anti-HAV IgM negative, anti HAV IgG positive. HBV DNA was negative.

Ultrasound of the abdomen showed liver of appropriate localization and shape, diameter of 155 mm and homogeneous parenchyma. To the left contour of the liver, around the pancreas, a few nodes was found with the largest diameter of

Table 1. Laboratory parameters during hospitalization of the patient

Laboratory parameter	Days of hospitalization						Reference values
	1st	2nd	7th	14th	21th	28th	
Leukocytes	3.97	4.20	4.43	6.95	7.75	4.1	4.0-10.0 10 ⁹ L ⁻¹
Erythrocytes	4.50	4.58	4.54	4.75	5.05	4.32	4.34-5.72x10 ¹² L ⁻¹
Hemoglobin	12.5	12.2	12.2	13.0	13.9	12.6	11.9-15.7 g d L ⁻¹
Platelets	119	123	91	181	101	121	150-400x10 ⁹ L ⁻¹
Glucose	6.5	6.3	11.7	21.8	16.7	7.7	3.3-6.1 mmol L ⁻¹
Urea	3.9				5.9		1.7-8.3 mmol L ⁻¹
Creatinine	58.0				36.0		79-125 mmol L ⁻¹
Bilirubin	149.1	277.7	260.5	93.5	61.4	37.8	1.1-18.8 μmol L ⁻¹
AST	941	945	414		26	28	0-38 U L ⁻¹
ALT	570	708	221		43	41	0-41 U L ⁻¹
LDH	302	339				255	135-225 U L ⁻¹
Albumin	32					34	34-48 g L ⁻¹
Globulin	47					47	21-39 g L ⁻¹
GGT	231					136	5-36 U L ⁻¹
ALP	217					130	35-120 U L ⁻¹
PT	90	74	100	59	105	100	70-120 %
INR	1.10	1.12	1.00	1.40	1.00	1.0	0.90-1.15 units INR
APTT	32.1	33.1	29.4	23.0	23.6	29	29-37 sec
TSH		0.27				0.03	0.34-5.6 μIU L ⁻¹
FT3		14.01				13.59	2.5-3.9 pmol L ⁻¹
FT4		2.64				3.67	0.58-1.64 pmol L ⁻¹

AST, serum aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; GGT, gamma glutamyl transpeptidase; ALP, alkaline phosphatase; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, thyroxine

33.3x10.3 mm. Gallbladder was in proper position, with thickened wall, with a little more dense content, and to the dorsal wall hyperechogenic structure size of 6.2 mm (calculus) was visible. The spleen was enlarged to 150 mm. Other findings were good.

A surgeon's examination and ultrasound of the abdomen excluded obstructive icterus. An ophthalmologist's examination (angiopathia hypertensive gr I/II) and copper levels of 17.7 μmol/L excluded hepatolenticular degeneration. Alpha-fetoprotein was 3.46 IU/mL and fibrinogen 3.10 g/L.

Immunohematological analyses showed slightly positive DAT, SCR on the irregular red cell antibodies I and II was negative, ANA slightly positive, AMA, ASMA, dsDNA, LKM-1, LC-1, SLA/LP, M2-3E (BPO), PML, Sp 100, gp210 immunological tests were negative. Immunoglobulin values found were as follows: IgG 15.4 g/L, IgA 2.0 g/L, IgM 0.6 g/L, IgE 167 IU/m.

During hospitalization the patient was occasionally sub-febrile, hypodynamic, frightened. The PTU was excluded immediately after admission, as well as propranolol, and the dosage of antidepressants was reduced. During the highest values

of bilirubin in the blood, corticosteroids were administered. During the seven-day corticosteroid treatment there was a significant improvement in liver function tests and transient increase in blood sugar (because insulin was included for a couple of days). In the second half of the hospitalization (from 6 August to 21 August) and at the time of discharge the patient was afebrile, only with mild clinical symptoms of hyperthyroidism. One month after the discharge from the hospital endocrinologist included thiamazole, weekly control of blood count and serum aminotransferase, which are still normal.

DISCUSSION

The clinical presentation of the liver damage caused by medication is very diverse and the diagnosis is not easy (13). It is a common occurrence of taking several different medications at the same time, which further complicates the detection of drug, which is responsible for liver damage. It is important to know in which time period from the beginning of taking the medication symptoms appeared to exclude alcoholic liver disease, cancers, autoimmune and viral hepatitis (13).

In the literature in recent years, there are different views of toxic damage to the liver with propylthiouracil. In most of them patterns of hepatocellular damage are described, besides cytotoxic effect, as a result of idiosyncrasy corresponding algorithms for the treatment were proposed (14,15). In China, from 2000 to 2013 on a sample of 8,864 patients with hyperthyroidism serious hepatotoxicity of propylthiouracil was observed in 90 patients (1.02%), more frequently in women (2.2:1), middle aged (41,6 years) and most often in the first three months of starting treatment (13). Although PTU-induced hepatotoxicity is rare and ranges from asymptomatic increase of aminotransferase to fulminant liver failure and death, the necessity of timely liver transplantation should always be considered (16).

In the literature case reports of hyperthyroidism with PTU toxic hepatitis and hepatitis B are rarely described. One of them (1990 from South Korea) describes a patient with chronic HBsAg carrier (HBsAg and anti-HBc positive, anti-HBc IgM, HBeAg and HBV DNA negative), which had hyperthyroidism and toxic hepatitis after two years of treatment with PTU and/or methimazole,

with acute hepatic failure and fatal outcome, but without reactivation of hepatitis markers of acute inflammation. Post-mortem liver biopsy showed micronodular cirrhosis with negative HBsAg and HBcAg in liver tissue (17).

The second case from 2008 is a case report of a patient with hyperthyroidism and PTU toxic hepatitis after two years of improper treatment, who had acute viral hepatitis B. The PTU was suspended, but because of goiter and extremely pathological values of thyroid hormone, the first plasmapheresis was made and then thyroid gland was removed surgically. On the fifth day after the surgery the patient's liver function improved and FT4 level was low. The work showed that plasmapheresis may be fast, reliable and effective way to reduce thyroid hormone in serum, allowing the successful thyroidectomy in patients with severe thyrotoxicosis (18).

Because of polymorphism of hardships in the past ten years, our patient had a real polypragmasy of drugs. She got the hyperthyroidism after recovered viral hepatitis B with HBsAg seroconversion (HBsAg negative, anti-HBs positive). The greatest potential for hepatotoxicity of all administered drugs probably should be referred

to PTU. During PTU toxic liver damage, there was no change of hepatitis markers and exacerbation of viral hepatitis B. The immune liver disease was excluded with negative autoantibodies and review of gastroenterohepatologist.

Both diseases, hypo- and hyperthyreosis are often associated with changes in liver function tests, so the thyroid diseases must be excluded at elevated serum aminotransferases of unknown cause (19). Also drugs, liver diseases, such as hepatitis, hepatocellular carcinoma, cirrhosis and alcoholic liver disease, can cause changes in thyroid hormone levels and be responsible for modified thyroid function (19). In conclusion, clinical practice should comprehensively monitor the effects of the intricate and tight connection between drugs, liver and endocrine system, in order to better resolve all manifestations, complications and worsening of one or another organic system.

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Competing interests: None to declare

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Povezanost prebolovanog hepatitisa B s nastankom toksičnog hepatitisa uzrokovanog propiltiouracilom

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SAŽETAK

Cilj Istražiti odnos između toksičnog hepatitisa uzrokovanog propiltiouracilom (PTU) i prebolovanog hepatitisa B, te ukazati na sve veći značaj upotrebe lijekova u nastanku hepatitisa.

Metode Prikazan je slučaj 45-godišnje bolesnice koja je, u zadnjih desetak godina, imala pravu polipragmaziju lijekova zbog polimorfizma tegoba (diabetes melitus, depresija, hipertenzija, hipertireoza).

Rezultati Hipertireozu je dobila nakon prebolovanog virusnog hepatitisa B sa HBsAg serokonverzijom (HBsAg negativan, antiHBs pozitivan). Najveći potencijal za hepatotoksičnost od svih ordiniranih lijekova imao je PTU. Nakon kortikosteroidne terapije došlo je do znatnog poboljšanja jetrenih testova. U toku bolesti nije došlo do promjene hepatitis-markera i egzacerbacije hepatitisa B.

Zaključak Klinička praksa mora cjelovito pratiti učinke zadržane i uske povezanosti lijekova, jetre i endokrinog sistema, kako bi bolje riješila sve manifestacije, komplikacije i pogoršanje jednog ili drugog organskog sistema.

KLjučne riječi: lijekovi, hepatotoksičnost, hipertireoza, HBsAg serokonverzija