Endocr (2010) 38:24–28
DOI 10.1007/s12020-010-9348-y

CASE REPORT AND REVIEW

Liver failure due to antithyroid drugs: report of a case and literature review

Sarantis Livadas · Xenofon Xyrafis · Frangiskos Economou · Georgios Boutzios · Maria Christou · Aristea Zerva · Athanasios Karachalios · Helen Palioura · Sotiria Palimeri · Evanthia Diamanti-Kandarakis

Received: 7 December 2009 / Accepted: 19 April 2010 / Published online: 18 May 2010

Abstract Hyperthyroidism is a common endocrine disorder affecting 2% of females and 0.5% of males worldwide and antithyroid drugs constitute the first line of treatment in the majority of cases. These agents may cause severe adverse effects and among them liver failure, although rare, is a potential lethal one. This case illustrates the sudden and abrupt deterioration of hepatic function due to antithyroid drug administration. This case along with a concise literature review is presented aiming to increase the awareness of endocrinologists of possible fatal complications from the everyday use of common agents such as antithyroid drugs.

Keywords Liver failure · Hyperthyroidism · Propylthiouracil · Methimazole · Transaminases · Thionamides

Introduction

Hyperthyroidism is a common disorder which in general affects approximately 2% of women and 0.2% of men [1], with an annual incidence of 30–100/100.000 in different countries [2, 3]. The side effects of antithyroid drugs, which constitute the universally accepted first line of treatment in hyperthyroidism, cover a wide spectrum from mild to severe and even unpredictably a fatal outcome (Table 1). Among them, hepatic failure is a rare life-threatening (0.1–0.2%) adverse reaction [4], but since physician's alert for this life-threatening condition may prevent progression, the presentation of this case and a review of appropriate literature are substantiated.

Case

A 34-year-old woman presented to the Endocrinology Unit due to tachycardia sweating, heat intolerance, palpitations, tiredness, hand tremor, and loss of body weight (4 kg) over the past 2 months. Her medical history was notable for polycystic ovary syndrome, under medication with OCP's over the past 10 years and from family history it must be reported that her father suffers from diabetes mellitus type 2. On physical examination, the patient was afebrile with a blood pressure of 120/80 mmHg and a pulse rate of 110 beats per minute. Thyroid gland was palpable, with diffused enlargement and a moderate holosystolic murmur. She had a moderate elevation of the right eyelid with lid lag and her hands were hot and moist with thin tremor. No pathological signs were detected from the other systems.

At the time of presentation, laboratory baseline values were compatible with hyperthyroidism [FT3 = 17.3 pg/ml (nv: 2.3–5.3), FT4 = 47.8 pmol/l (nv: 10–25), and TSH = 0.047 mu/l (nv: 0.3–4)], followed with normal liver values. The patient was advised to stop the OCP's medication and start treatment with antithyroid drugs and beta-blockers on the following regimen: methimazole 20 mg S:1 × 3 and propranolol 40 mg, S:1/2 × 3.

S. Livadas · X. Xyrafis · F. Economou · G. Boutzios · M. Christou · A. Zerva · A. Karachalios · H. Palioura · S. Palimeri · E. Diamanti-Kandarakis
Endocrine Section, First Department of Internal Medicine, Laiko General Hospital, Medical School, University of Athens, Athens, Greece

E. Diamanti-Kandarakis (✉)
University of Athens Medical School, Mikras Asias 75, Goudi 115-27 Athens, Greece
e-mail: akandara@otenet.gr

Table 1 Side effect of antithyroid drugs

Side effect	Frequency
Skin reactions	4–6%
Arthralgias	1–5%
Gastrointestinal effects	1–5%
Polyarthritis	1–2%
Agranulocytosis	0.1–0.5%
Hepatitis	0.1–0.2%
Abnormal sense of taste or smell	Rare
ANCA–positive vasculitis	Rare
Cholestasis	Rare
Hypoprothrombinemia	Rare
Hypoglycemia	Rare
Other hematologic effects	Very rare
Pancreatitis	Very rare
Sialadenitis	Very rare

Twenty days post treatment initiation the patient reported pruritus. Laboratory testing revealed a moderate elevation of the serum transaminases accompanied with slight elevation of γ-GT and biochemical improvement of hyperthyroidism (TSH = 0.1 mu/l, FT3 = 6.3 pg/ml, FT4 = 29 pg/ml). Liver dysfunction was attributed to methimazole: thus antithyroid treatment was switched to propylthiouracil (50 mg S:2 × 3). However, close monitoring of liver biochemistry on outpatient basis showed progressive worsening and accordingly the patient was admitted to our department.

At the time of admission the patient suffered from pruritus which over the past 5 days became more intensive in the hands and pelmas. A papulus rash was apparent in the flexory surfaces of antebrachium, neck, abdomen, and in the outer thighs. She reported anorexia and dizziness. Her skin and sclerae were jaundiced, moderate depigmentation of the stools and hyperpigmentation of the urine were apparent. Physical examination revealed jaundiced skin with normal turgor, clear breath sounds and cardiac tones, soft abdomen with just palpable in deep breath spleen. Liver was palpable with a smooth, painful edge. The blood pressure was 125/70 mmHg and the pulse rate 80/min. Moderate elevation of the right eyelid was observed with lid lag.

Ultrasonography of the upper abdomen showed increased liver size with patchy composition. No sign of intrahepatic biliar dilatation was found and hepatic virus inspection was negative. Specifically, the following antibodies were found negative: HBs Ag, HBs Ab, HBc Ab, HCV, HIV, EBV, CMV, Toxo.

The patient was prescribed propranolol, antihistamine per os, cortisol IV, and iodine drops. Ten days post admission a total thyroidectomy was carried out. The histological examination confirmed diffuse toxic goiter on regression (Grave's disease) and a microscopic lesion of papillary carcinoma with maximum diameter of 0.4 cm. The postoperative course of the patient was uneventful and transaminases values gradually returned to normal. Laboratory profile and hepatic enzyme biochemistry are analytically depicted in Table 2 and Fig. 1.

Discussion

In the case presented, we portray a young woman with Grave's disease who developed serious liver damage, which could be attributed to both categories of antithyroid drugs. Specifically, the patient was prescribed methimazole initially on hyperthyroidism diagnosis, but because of development of jaundice and pruritus accompanied with significantly increasing values of aminotransferases, the patient was switched to propylthiouracil. However, the

Table 2 Laboratory testing of the patient before and during hospitalization

Parameters studied (normal values)	Switching from MMI to PTU	Day 1	Day 3	Day 5	Day 7	Day 9	Day 12
Ht (%)/Hb (g/dl)	38/12.5	39.8/13.1	38.4/13	38.2/12.6	42.4/14	42.2/14.3	42.5/14.2
WBC (K/Ul)	6.600	8.200	13.880	17.000	18.740	18.070	19.300
PLT (K/μl)	450.000	514.000	534.000	527.000	533.000	427.000	451.000
PT (sec)	10.2	10.0	13.2	13.3	13.3	12.5	12.6
Tot. bilirubin (0.2–1.2 mg/dl)	2.4	3.6	2.19	1.38	1.43	0.96	1.01
Dir. bilirubin (<0.2 mg/dl)	1.6	2.7	1.43	0.89	0.8	0.63	0.55
ALP (64–280 IU/l)	120	189	396	270	269	184	217
γGT (7–32 IU/l)	56	74	71	69	99	85	91
AST (10–48 IU/l)	60	339	255	95	56	31	35
ALT (10–40 IU/l)	141	951	1125	697	469	196	189
LDH (200–460 IU/l)	105	539	412	283	244	241	235
CPK (20–190 IU/l)	10	11	17	17	22	12	15

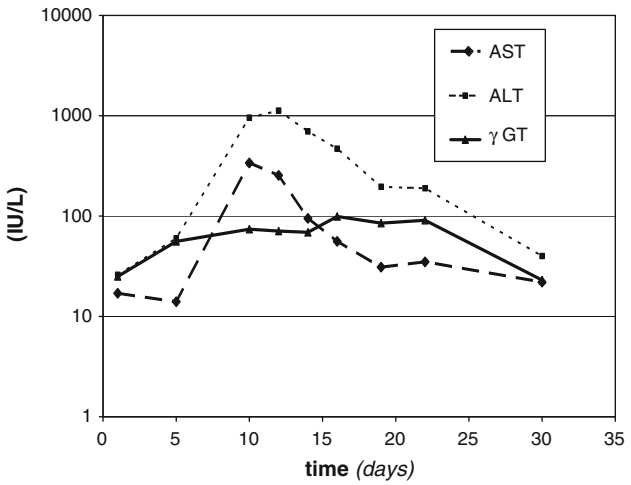

Fig. 1 Liver biochemistry values during follow-up

progression of the disease was not suspended, making the surgical management of hyperthyroidism with the continuous administration of cortisol, iodine, and antihistamine drugs, the only therapeutic solution.

Hepatotoxicity is a rare but major side effect of antithyroid drugs. The estimated incidence of antithyroid drug-associated hepatotoxicity ranges from 0.1% to 0.2%, although the true incidence is unknown [4]. Drug-induced hepatocellular injury is a difficult diagnosis to establish and is often one of exclusion. Ideal and practical criteria were proposed by Hanson [5], in 1984 to assist in the diagnosis of drug-induced hepatitis. However, only the histological confirmation of hepatocellular injury and drug re-challenge would establish the diagnosis, but this is seldom ethically and practically possible [6]. The patient presented in this case fulfilled the diagnostic criteria of drug-induced hepatotoxicity. In relation to the current illness, viral hepatitis infection was excluded by serological determinations (hepatitis A, B, C, CMV, Toxo, and EBV) and there was no history of chronic liver disease, alcohol abuse, or drug use. In addition, oral contraceptive pills had been discontinued 20 days prior to the elevation of liver enzymes, when hyperthyroidism was diagnosed.

Antithyroid drugs, known as thionamides, contain a sulfhydryl group and a thiourea moiety within a heterocyclic structure. Thionamide compounds inhibit thyroid hormone synthesis as they are actively transported into the thyroid gland, where they inhibit both the organification of iodine to tyrosine residues in thyroglobulin and the coupling of iodotyrosines. Thionamides are propylthiouracil (6-propyl-2-thiouracil) and methimazole (1-methyl-2 mercaptoimidazole). Carbimazole is an imidazole antithyroid agent under a class of drugs known as pro-drugs and it is considered a pro-drug because it converts rapidly to methimazole after being absorbed by the body [7].

The rare hepatic abnormalities associated with methimazole (and carbimazole) are typical of a cholestatic process. In a small number of cases of presumed methimazole-induced liver dysfunction, an elevation of bilirubin was the major abnormality and in most of these case reports, mild elevations in liver enzymes and bilirubin occurred within 2 weeks of initiation of methimazole therapy and in liver biopsy specimens preserved hepatocellular architecture along with intracanalicular cholestasis and mild periportal inflammation was observed. Complete, slow recovery is the rule after drug discontinuation [8–17].

The side effects of methimazole are dose-related and hepatic toxicity with methimazole is not as severe as the potentially life-threatening hepatocellular reactions that are seen with propylthiouracil. Liver damage induced from propylthiouracil has been considered to be an allergic host response, immune-mediated, as evidenced by the observation that toxic symptoms occurred at an accelerated rate on re-challenge with antithyroid drugs [18–20]. In addition, peripheral lymphocyte sensitization to propylthiouracil has been demonstrated in vitro [21, 22]. Propylthiouracil-induced severe hepatitis does not seems to be associated with a high dose of the drug and it must be mentioned that elevated liver enzymes in thyrotoxicosis have been shown not to be predictive of further increases after the institution of propylthiouracil therapy [18, 23].

The mechanism via which propylthiouracil causes hepatocyte malfunction has been investigated in experimental animals and has shown to decrease rat hepatic cytochrome P-450 levels and to inhibit benzphetamine metabolism. These findings suggest that the active metabolites of propylthiouracil may interact with the macromolecules of the endoplasmic reticulum and lead to centrilobular hepatic necrosis. Interestingly, evidence has shown that propylthiouracil forms active metabolites that may lead to centrilobular hepatic necrosis. Conceivably, hepatic injury due to metabolites of propylthiouracil may also occur in humans [24, 25]. Because of the possible autoimmune etiology of propylthiouracil hepatotoxicity and recurrence of hepatotoxicity with drug rechallenge, propylthiouracil should not be reinstituted even after resolution of hepatotoxicity or liver transplantation.

The recognition of propylthiouracil-related hepatoxicity constitutes a difficult task, since in up to 30% of patients with normal baseline aminotransferase levels who are treated with propylthiouracil, transient acute increases in those levels develop, ranging from 1.1 to 6 times the upper limit of normal—levels that resolve while therapy is continued [26]. The percentage of patients with AST and ALT higher than twice the upper range of the normal range was 26.9% on propylthiouracil 300 mg/d, compared with only 6.6% on methimazole 30 mg/d [27]. Although propylthiouracil commonly induces subclinical and asymptomatic

liver injury, liver damage is usually transient, and propylthiouracil may be continued with caution in the absence of symptoms and hyperbilirubinemia. It should be emphasized that literature data suggest a case fatality rate of 25–50%, however, it is likely that milder cases that resolve uneventfully are never reported [28, 29]. Nevertheless, recent data suggest that in children and pregnant women more caution during propylthiouracil administration is needed [30–32].

Liver transplantation and/or plasmapheresis may be required, and referral to a specialized center is reasonable. Of the 10 documented cases of propylthiouracil-induced hepatitis in which liver biopsies were taken, histopathologic features have ranged from mild portal inflammation to submassive or massive hepatic necrosis with bridging fibrosis [33–35].

Since the mechanisms of hepatotoxicity for the two antithyroid drugs differ, the alternative agent can be used cautiously to treat the underlying hyperthyroidism. However, in the present case after 2 days of propylthiouracil administration the laboratory evaluation showed marked elevation of aminotransferases and worsening hyperbilirubinemia. Propylthiouracil was discontinued and intravenous hydrocortisone was started and within 48 h, an improvement was noted in laboratory values. Whether this improvement was due in part to the steroid therapy or simply to the discontinuation of antithyroid drugs is unclear. However, the successful use of steroid has been reported for fulminant hepatitis caused by antithyroid agents. It must be emphasized that the type of hepatic injury in steroid-responsive cases was hepatocellular [36, 37]. Further studies are needed on the mechanisms of antithyroid drugs causing hepatotoxicity and on the use of steroid in these conditions.

In this case, methimazole could be considered as the cause of hepatotoxicity. Nevertheless, since the interval from the beginning of propylthiouracil administration to the onset of the liver damage varies from 1 day to 14 months, propylthiouracil cannot be excluded as a possible cause [38]. However, in most patients, the interval is within 5 months most frequently been within 3 months [39]. In addition, the possibility of crossover reactivity between the two drugs cannot be excluded too, since cross-sensitivity has been reported to occur in about 50% of patients and additionally cross-reactivity of the two drugs causing hepatotoxicity has also been reported [40, 41]. The type of liver injury in patients receiving propylthiouracil and methimazole (or carbimazole) was usually hepatitic or mixed cholestatic hepatitis. In one case of liver failure due to concomitant administration of propylthiouracil and methimazole liver biopsy revealed portal inflammatory changes and hepatocyte necrosis, with or without intracanalicular cholestasis [42].

Finally, considering thyrotoxicosis and its impact on liver biochemistry, it is known to cause a variety of non-specific abnormalities in liver tests. It has been reported that up to 72% of patients with hyperthyroidism and presumably normal liver function may have an elevation of at least one hepatic enzyme, probably due to increased hepatic oxygen consumption without increased hepatic blood flow, leading to hepatic dysfunction [43, 44]. In addition, some research groups have supported the idea that an underlying defect in bilirubin metabolism is the cause of cholestasis observed in hyperthyroidism, whereas others have proposed that the hepatic dysfunction is due to overt or occult congestive heart failure [45, 46]. However, evidence for a direct toxic effect of thyroid hormones on liver cells has not been documented [44]. Jaundice is an uncommon finding in patients suffering from hyperthyroidism and it has been related to congestive heart failure and secondary hepatic dysfunction [47].

In conclusion, since early recognition of antithyroid drug-induced hepatic failure and prompt withdrawal of the drug may prevent progression from mild to severe disease, it may be useful to discuss signs and symptoms of liver disease and other side effects with patients. Jaundice, pruritus, dark urine, abdominal pain, anorexia, or malaise should alarm the patient to seek medical advice. Routine monitoring of liver-function tests in patients being treated with propylthiouracil is generally not recommended, given the frequent benign liver-function abnormalities noted earlier. However, the physician should be alert and evaluate liver biochemistry in case of clinical suspicion.

References

1. J. Franklyn, Clin. Med. **3**, 11–15 (2003)
2. M. Abraham-Nordling, O. Törring, M. Lantz, B. Hallengren, H. Ohrling, G. Lundell, J. Calissendorff, G. Jörneskog, G. Wallin, Eur. J. Endocrinol. **158**, 823–827 (2008)
3. M.P. Vanderpump, W.M. Tunbridge, J.M. French, D. Appleton, D. Bates, F. Clark, J. Grimley Evans, D.M. Hasan, H. Rodgers, F. Tunbridge, E.T. Young, Clin. Endocrinol. **43**, 55–68 (1995)
4. D.S. Cooper, Endocrinologist **9**, 457–476 (1999)
5. J.S. Hanson, Arch. Intern. Med. **144**, 994–996 (1984)
6. R. Malik, H. Hodgson, QJM **95**, 559–569 (2002)
7. D.S. Cooper, N. Engl. J. Med. **352**, 905–917 (2005)
8. D.M. Arab, D.A. Malatjalian, R.S. Rittmaster, J. Clin. Endocrinol. Metab. **80**, 1083–1085 (1995)
9. M.G. Fisher, H.R. Naylor, A. Miller, JAMA **223**, 1028–1029 (1973)
10. G. Luca, S. Orietta, P. Caterina, S. Giovambattista, F. Maria, Curr. Drug Saf. **4**, 204–206 (2009)
11. M. Majeed, A. Babu, Am. J. Med. Sci. **332**, 51–53 (2006)
12. N.E. Mikhail, South Med. J. **97**, 178–182 (2004)
13. L.S. Ramos-Bonner, T.H. Goldberg, S. Moyer, C. Anastasopoulou, Am. J. Geriatr. Pharmacother. **5**, 236–240 (2007)
14. C. Ayensa, R. Diaz de Otazu, J.M. Cia, Arch. Intern. Med. **146**, 1455 (1986)

15. H. Blom, J. Stolk, H.B.,v. Schreuder, M. van der von Blomberg-Flier, Arch. Intern. Med. **145**, 1513–1515 (1985)
16. W.W. Dinsmore, M.D. O'Hara, M.E. Callender, N. Engl. J. Med. **309**, 438 (1983)
17. G. Ozenne, N.D. Manchon, J. Doucet, J. Hemet, J.C. Schrub, E. Bercoff, J. Clin. Gastroenterol. **11**, 95–97 (1989)
18. M. Weiss, D. Hassin, H. Bank, Arch. Intern. Med. **140**, 1184–1185 (1980)
19. B.Z. Garty, R. Kauli, J. Ben-Ari, E. Lubin, M. Nitzan, Z. Laron, Drug Intell. Clin. Pharm. **19**, 740–742 (1985)
20. C.Y. Hayashida, A.J. Duarte, A.E. Sato, E.H. Yamashiro-Kanashiro, J. Endocrinol. Invest. **13**, 937–941 (1990)
21. A.A. Mihas, P. Holley, R.S. Koff, B.I. Hirschowitz, Gastroenterology **70**, 770–774 (1976)
22. F. Pacini, V. Sridama, S. Refetoff, J. Endocrinol. Invest. **5**, 403–407 (1982)
23. A. Gurlek, V. Cobaukara, M. Bayraktar, J. Clin. Gastroenterol. **24**, 180–183 (1997)
24. A.L. Hunter, R.A. Neal, Biochem. Pharmacol. **24**, 2199–2205 (1975)
25. D.S. Seidman, E. Livni, B. Ilie, I. Blum, J. Toxicol. Clin. Toxicol. **24**, 353–360 (1986)
26. Y.F. Liaw, M.J. Huang, K.D. Fan, K.L. Li, S.S. Wu, T.J. Chen, Ann. Intern. Med. **118**, 424–428 (1993)
27. H. Nakamura, J.Y. Noh, K. Itoh, S. Fukata, A. Miyauchi, N. Hamada, J. Clin. Endocrinol. Metab. **92**, 2157–2162 (2007)
28. J.K. Ruiz, G.V. Rossi, H.A. Vallejos, R.W. Brenet, I.B. Lopez, A.A. Escribano, Ann. Pharmacother. **37**, 224–228 (2003)
29. A. Limaye, P.R. Ruffolo, Am. J. Gastroenterol. **82**, 152–154 (1987)
30. S.A. Rivkees, NEMJ **360**, 1574–1575 (2009)
31. D.S. Cooper, S.A. Rivkees, J. Clin. Endocrinol. Metab. **94**, 1881–1882 (2009)
32. Propylthiouracil-related liver toxicity (Public Workshop, Washington, D.C. April 18, 2009) www.fda.gov/CDER/meeting/ptu_toxicity.htm
33. B. Baker, B. Shapiro, L.M. Fig, D. Woodbury, J.C. Sisson, W.H. Beierwaltes, Thyroidology **1**, 17–26 (1989)
34. M. Enghofer, K. Badenhoop, S. Zeuzem, A. Schmidt-Matthiesen, C. Betz, A. Encke, K. Henning, J. Clin. Endocrinol. Metab. **85**, 1765–1769 (2000)
35. M. Levy, Clin. Pediatr. **32**, 25–29 (1993)
36. Y. Ichiki, M. Akahoshi, N. Yamashita, C. Morita, T. Maruyama, T. Horiuchi, K. Hayashida, H. Ishibashi, Y. Niho, J. Gastroenterol. **33**, 747–750 (1998)
37. D.R. Lock, Z.M. Sthoeger, J. Clin. Gastroenterol. **24**, 267–269 (1997)
38. K.V. Williams, S. Nayak, D. Becker, J. Reyes, L.A. Burmeister, J. Clin. Endocrinol. Metab. **82**, 1727–1733 (1997)
39. L. Bartalena, M.L. Tanda, F. Bogazzi, E. Piantanida, A. Lai, E. Martino, Expert Opin. Pharmacother. **6**, 851–861 (2005)
40. J.L. Sadoul, B. Canivet, P. Freychet, Eur. J. Med. **2**, 473–477 (1993)
41. A. Chan, I. Ng, C.M. Lam, T.W. Shek, C.L. Lai, Hong Kong Med. J. **9**, 377–380 (2003)
42. M.J. Huang, K.L. Li, J.S. Wei, S.S. Wu, K.D. Fan, Y.F. Liaw, Am. J. Gastroenterol. **89**, 1071–1076 (1994)
43. R. Salata, I. Klein, G.S. Levey, Semin. Liver Dis. **5**, 29–34 (1985)
44. N.J. Greenberger, F.D. Milligan, L.J. DeGroot, K.J. Isselbacher, Am. J. Med. **36**, 840–846 (1964)
45. S. Sherlock, *Diseases of the liver and biliary system*, 7th edn. (Blackwell, Boston, 1985), pp. 399–400
46. D.C. Beaver, J. Pemberton, Ann. Intern. Med. **7**, 687–708 (1993)
47. H.P. Dooner, J. Parada, C. Aliaga, C. Hoyl, Arch. Intern. Med. **120**, 25–32 (1967)