Clinical Case Report

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Methimazole-induced liver injury overshadowed by methylprednisolone pulse therapy

Case report

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Abstract

Rationale: Treatment choices are limited, when deciding how to manage thyrotoxicosis and moderate to severe Graves ophthalmopathy (GO) with suspected optic nerve damage in patients with elevated liver transaminase levels. The situation become even more complicated, if methimazole induced hepatotoxicity is suspected and intravenous methylprednisolone is co-administrated.

Patient concerns: A 74-year-old woman presented with spontaneous retro-bulbar pain, eyelid swelling and inconstant diplopia.

Diagnoses: Thyrotoxicosis and severe GO with suspected optic nerve damage and drug induced liver injury (DILI).

Interventions: Intravenous methylprednisolone pulse therapy was administered to treat GO and methimazole was continued for thyrotoxicosis. Dose of methimazole was reduced after exclusion of concurrent infection and active liver disease.

Outcomes: The GO symptoms (eyelid swelling, sight loss, proptosis, retro-bulbar pain, diplopia) markedly decreased after the treatment course. Liver transaminases spontaneously returned to normal ranges and remained normal during the next 12 months until the Graves' disease until the treatment was completed.

Lessons: 1. The interaction of methimazole and methylprednisolone may result in DILI. 2. In a patient without concomitant liver diseases MP can be continued if the methimazole dose is reduced if no other treatment options are available.

Abbreviations: AH = autoimmune hepatitis, ALT = alanine transaminase, AST = asparagine transaminase, DILI = drug-induced liver injury, GO = Graves ophthalmopathy, MILI = methylprednisolone-induced liver injury, MP = methylprednisolone, ULN = upper limit of normal.

Keywords: Graves ophthalmopathy, intravenous methylprednisolone pulse therapy, methimazole

1. Introduction

It is generally believed that intravenous glucocorticoid therapy for Graves disease accompanied by Graves ophthalmopathy (GO) rarely causes acute liver injury, provided that the patients are appropriately selected, an active liver disease is excluded, and the cumulative dose of intravenous methylprednisolone (MP) does not exceed 8 g in 1 course of therapy. A number of researchers have described several cases of acute liver damage with intravenous glucocorticoids (GC) including a few cases of fatal outcomes.[1,2] Treatment with methimazole has also been associated with transient, asymptomatic elevations in serum aminotransferases levels. There are different guidelines, and firm rules are lacking in decision-making regarding the withdrawal of the offending drug. ACG Clinical Guideline on the Diagnosis and Management of Idiosyncratic Drug-induced liver injury (DILI) recommends to stop the suspected agent(s) in individuals with suspected DILI, especially when liver biochemistries are rising rapidly or there is evidence of liver dysfunction.[3] In addition, it is known that discontinuation of the offending medication will lead to a resolution of any injury within a few weeks, especially in the case of hepatocellular injury.[4] Such approach may not always be optimal, if the offending drug is indeed indispensable (in sensu lato). To avoid unnecessary drug withdrawal, the International Serious Adverse Events Consortium recommended in 2011 the modified biochemical criteria for the identification of DILI as reaching any of the following items: (1) alanine transaminase (ALT) ≥5 upper limit of normal (ULN); (2) alkaline phosphatase (ALP) ≥2 ULN, especially in patients with elevated 5′-nucleotidase or gamma-glutamyl transferase, and without bone diseases-related ALP elevation; (3) ALT ≥3 ULN and total bilirubin (TBil) ≥2 ULN.[5,6] In addition, it is generally agreed that suspected offending drugs are to be discontinued if (1) serum ALT or asparagine transaminase (AST) >8 ULN; (2) ALT or AST >5 ULN, which lasts for 2 weeks; (3) ALT or AST >3 ULN, with TBil >2 ULN or INR >1.5; (4) ALT or AST >3 ULN, which is accompanied by gradually aggravated fatigue, digestive tract

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The data regarding the time course of described events is provided in the supplementary material.

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symptoms, and/or increased percentage of eosinophils (>5%).[5] This recommendation reflects similar views to previously published ones).[7]

As a result, clinicians are faced with the dilemma whether to continue methimazole with MP and to risk further liver damage, or to devise an alternative approach, bearing in mind that treatment with methimazole and MP is often the only treatment for Graves disease accompanied by moderate to severe GO with suspected optic nerve damage. We present a case of DILI during GO treatment with methimazole and intravenous MP pulse therapy, where continuation of methimazole and MP did not cause any further liver damage and resulted in successful receding of both DILI and GO symptoms. Furthermore, we investigate potential mechanisms of methimazole and MP.

2. Case presentation

A 74-year-old woman was hospitalized in the Clinic for Endocrinology of the University hospital because of worsening of GO symptoms persisting for a few months. The patient was diagnosed with Graves disease for 6 months. The diagnosis was confirmed by elevated free thyroxine (fT4) 48.1 pmol/l (reference range: 10.0–22.0) and free triiodothyronine (fT3) 6.2 pmol/L (reference range: 2.5–5.8) levels, decreased thyroid-stimulating hormone 0.005 mUI/L (reference range: 0.27–3.75), and elevated levels of thyroid antibodies—thyrotropin receptor antibodies 14.9 U/L (reference range: <9) and thyroid peroxidase antibodies 56 kU/L (reference range: 0–12). The patient started her treatment with methimazole 30 mg/d 6 months before she was admitted, and gradually a maintenance dose of 10 mg/d was achieved by tapering and monitoring of the thyroid function over 2 months. The patient was a nonuser of alcohol and tobacco.

The patient experienced gradually progressing GO symptoms: spontaneous retro-bulbar pain, eyelid swelling, and inconstant diplopia. A consulting ophthalmologist identified proptosis (left eye 25.0 mm, right eye 21.5 mm), a moderate swelling of the eyelids, and redness in both eyes. Optic nerve involvement was suspected because of the observed decrease in the visual acuity. The patient was diagnosed with active moderately severe GO. An orbital computer tomography scan revealed an enlargement of eye muscles in both eyes, which was more severe in the left eye. However, compression of the optic nerves was not confirmed. The presence of concurrent infection and active liver disease was excluded, and the patient received MP therapy (500 mg per week for 6 weeks and 250 mg per week for 6 weeks) in conjunction with methimazole 10 mg p/o daily. Liver function tests, glucose, urinary analysis, and complete blood count were evaluated before each MP pulse. Hepatitis B and C testing (anti-surface antigen of the hepatitis B virus and anti-hepatitis C virus) results excluded hepatic viral infections. Baseline evaluations of liver function tests, subsequent results of liver enzymes, and the total cumulative dose of administered methimazole are provided in enclosed documents.

Clinical signs of GO started to improve after the first 2 MP courses: there was a decrease in the spontaneous retro-bulbar pain and eyelid swelling, and the visual acuity improved. A slight elevation of ALT was identified after the fourth MP course with a subsequent elevation of 3 times the ULN. AST rose more than twice the upper limit and iatrogenic hypothyroidism fT3 2.15 pmol/L (reference range: 2.5–5.8) and fT4 7.31 pmol/L (reference range: 10.0–22.0) was diagnosed before the fifth MP pulse. The results of liver function tests (prothrombin time, activated partial thromboplastin time and international normalized ratio, direct and conjugated bilirubin and albumin levels) were within the normal range. The treatment with methimazole and MP was continued, though methimazole dosage was reduced to 5 mg once daily. Abdominal sonography revealed no abnormal changes in the liver. The markers of autoimmune hepatitis (AH) were negative, antimitochondrial antibodies 1:40, antinuclear antibodies 1:40, and the serum protein electrophoresis were normal. The patient did not start any new medicines or food supplements, and no other health changes were observed. Secondary diabetes mellitus was confirmed before the sixth MP course. After the pulse, the transaminase levels were little bit lower than before the MP therapy. That was also observed during the fifth, sixth, seventh, eighth, and ninth pulses. Transaminases reached the highest level before and after the fifth and sixth pulses, and then spontaneously returned to normal ranges and remained normal during the remaining MP pulse therapy courses. ALT was the first to start increasing and the last to return to normal level. No abnormalities were revealed by other liver tests.

From the eighth MP to the end of the GO treatment and 12 months after the end of the MP pulse therapy, euthyrosis was maintained with 2.5 mg of methimazole daily. The GO symptoms (eyelid swelling, sight loss, proptosis, retro-bulbar pain, diplopia) markedly decreased after the treatment course, and after the GO reassessment the criteria of mildly inactive GO were satisfied. Secondary diabetes mellitus receded 4 months after the MP pulse therapy ended. No transaminase elevations were observed during the next 12 months until the Graves disease treatment was completed (Table 1).

3. Discussion

Graves ophthalmopathy is an autoimmune disease requiring maintenance of normal thyroid function with antithyroid drugs and, in the case of active moderate severe or severe GO, a high-dose intravenous glucocorticoid pulse therapy.

Drug-induced hepatotoxicity is defined as hepatocellular injury indicated by leakage of aminotransferase enzymes from injured liver cells without clear evidence of hepatobiliary obstruction or intrahepatic cholestasis.[8] Methimazole and MP (in pulse therapy doses) are drugs that can potentially induce hepatocellular injury. Thus, during the course of GO and thyrotoxicosis treatment, a number of questions needed to be addressed:

(1) What caused the rise in aminotransferase levels?
(2) Should the methimazole and MP pulse therapy be discontinued?
(3) Is the benefit–risk ratio of the treatment continuation still favorable even if the liver transaminase levels markedly increase?

These are important questions in view of the limited, treatment options for both conditions—thyrotoxicosis and GO: treatment with available thyrostatics (propylthiouracil and methimazole)[9] entails the risk of liver injury, treatment with surgery is not an optimal choice unless euthyrosis is reached, treatment with radioiodine is contraindicated in patients with severe GO, whereas treatment of moderate severe GO in patients with suspected optic nerve damage has also no alternatives for intravenous GC.

However, treatment with methimazole has the potential to cause hepatocellular DILI. It is defined as leakage of aminotransferase enzymes from injured liver cells without a prominent evidence of hepatobiliary obstruction or intrahepatic cholestasis, and usually presents itself with cholestatic syndrome[10,11] or

Table 1

Timetable of events.

Dates	Summaries from initial and follow-up visits	Diagnostic testing (including dates)	Interventions
February 26, 2015	Manifestation of Graves ophthalmopathy. Symptoms: spontaneous retro-bulbar pain, eyelid swelling, inconstant diplopia. Clinically apparent proptosis. Decrease in visual acuity	February 26, 2015: Orbital computer tomography scan: the enlargement of eye muscles in both eyes, more severely in the left eye, but the compression of the optic nerves was not confirmed. February 26, 2015: AST 16 (n = 0–31) IU/L, ALT 16 (n = 0–34) IU/L, GGT 0 (n = 0–38) IU/L, ŠF 59 (n = 32–91) IU/L	Methylprednisolone 500 mg infusion twice (27 February, 2015 and March 2, 2015); methimazole 5 mg b.i.d. cumulative dose 7870 mg over 57.29 wks.
March 5, 2015	Patient complains of itching in the ocular area.	AST 16 (normal range 0–35 U/L) ALT 16 (normal range 0–35 U/L) γ-GT 0 (normal range 8–78 U/L) AP 59 (normal range 36–92 U/L)	Methylprednisolone 500 mg infusion; methimazole 5 mg b.i.d.
March 12, 2015	The patient reported decreased eye symptoms	AST 12 (normal range 0–35 U/L) ; ALT 20 (normal range 0–35 U/L); γ-GT 0 (normal range 8–78 U/L); AP 58 (normal range 36–92 U/L)	Methylprednisolone 500 mg infusion; methimazole cumulative dose 7900 mg
March 19, 2015		AST 17 (normal range 0–35 U/L); ALT 18 (normal range 0–35 U/L); γ-GT 0 (normal range 8–78 U/L) AP 63 (normal range 36–92 U/L)	Methylprednisolone 500 mg infusion; methimazole cumulative dose 8010 mg
March 26, 2015		AST U/I 23 (normal range 0–35 U/L); ALT 37 (normal range 0–35 U/L)	Methylprednisolone 500 mg infusion; methimazole cumulative dose 8090 mg. Methimazole dose reduction to 5 mg once daily.
April 2, 2015		AST 94–61 (normal range 0–35 U/L ALT 164–156 (normal range 0–35 U/L) Liver function tests (prothrombin time, activated partial thromboplastin time and international normalized ratio, direct and conjugated bilirubin and albumin levels) were performed and were within normal range Hepatic viral infections were excluded by testing for hepatitis B and C: anti-HBsAg and anti-HCV. Abdominal sonography revealed no abnormal changes in the liver. The markers of autoimmune hepatitis were negative, anti-mitochondrial antibodies (AMAs) 1:40, anti-nuclear antibodies (ANAs) 1:40 and electrophoresis of serum protein was normal.	Methylprednisolone 500 mg infusion; Methimazole cumulative dose 8150 mg.
April 9, 2015		AST 89–53 (normal range 0–35 U/L) ALT 194–167 (normal range 0–35 U/L)	Methylprednisolone 500 mg infusion; Methimazole cumulative dose 62.43 wks, 8190 mg
April 16, 2015		AST U/I 45–30 (normal range 0–35 U/L) ALT 126–93 (normal range 0–35 U/L	Methylprednisolone 500 mg infusion; Methimazole cumulative dose 8207.5 mg
April 23, 2015		AST U/I 27–19 (normal range 0–35 U/L) ALT 59–47 (normal range 0–35 U/L	Methylprednisolone 500 mg infusion; Methimazole cumulative dose 8225 mg

Relevant past medical history and intervention: 74-year-old woman was diagnosed with Graves disease in 2014. The patient was using methimazole 5 mg b.i.d. 2015.01.21 free thyroxine (fT4) 48.1 pmol/L (reference range: 10.0–22.0) and free triiodothyronine (fT3) 6.2 pmol/L (reference range: 2.5–5.8) levels, decreased thyroid-stimulating hormone (TSH) 0.005 mUI/L (reference range: 0.27–3.75), elevated levels of thyroid antibodies—the thyrotropin receptor antibodies (TRAbs) 14.9 U/L (reference range: <9), the thyroid peroxidase (TPO) antibodies 56 kU/L (reference range: 0–12) kU/L. GGT = gamma-glutamyl transferase, HBsAg = surface antigen of the hepatitis B virus.

with transient, asymptomatic elevations in serum aminotransferase levels, typically from 2 days to 3 months of administration. Inasmuch as these changes are usually clinically insignificant, even therapy continuation can lead to their resolution.[12–15] The severity of methimazole-induced liver injury varies from mild, transient serum aminotransferase elevations to moderately severe cholestatic hepatitis.[16] However, researchers have also reported some fatal cases of methimazole-induced DILI.[17] Recent research focuses on several mechanisms of methimazole-induced liver injury [18]: relative hypoxia of the portal system causing hepatocyte degeneration and necrosis, direct toxic effect of methimazole metabolite (eg, generation of sulfenic acids,[9] allergic reactions, immune-mediated DILI, such as hapten hypothesis,[9] or an exacerbation of individual bile metabolic disorders [Gilbert syndrome]).[10,18] The same is true in case of propylthiouracil.[19]

It is generally believed that GO treatment with intravenous GC rarely causes acute liver injury, provided that patients are appropriately selected, an active liver disease is excluded, and the cumulative dose of intravenous MP does not exceed 8 g in 1 course of the therapy.[20] Where the patient follows expert's recommendations for severe GO treatments with the total MP dose of 4.5 g, the adverse event risk is very low. However, treatment for other autoimmune diseases requires much higher doses of MP pulses and increases the risk of all adverse events, including MP-induced liver injury (MILI).[21] MILI is usually idiosyncratic and occurs within 3 days to 6 weeks, although it may manifest even 6 months after drug discontinuation.[22,23] Previous studies have reported several fatal outcomes due to acute liver damage linked to the use of intravenous GC.[1,2] Nevertheless, such outcome is rare with the prevalence rate of approximately 1%.[23] According to the global adverse drug reaction surveillance, clinically manifest hepatotoxicity is considered a probable adverse reaction of high-dose MP (at least 2000 mg during at most 31 days).[21]

In our case, the patient received methimazole for a period of about 61 weeks with a total cumulative dose of 7870 mg, and no liver function abnormalities were identified before the MP treatment. Only in week 5 of the MP pulse therapy the ALT levels started to increase, when the cumulative dose of MP reached 2000 mg over 28 days. To diagnose DILI, we excluded AH and viral hepatitis as MP can reactivate HBV infection or induce exacerbation of HCV infection.[24,25]

In reviewing the literature, the risk of DILI development as a result of using each medicine separately was found to be very low. However, several studies present supporting data regarding potentially increased risk of DILI due to the interaction of methimazole and MP as explained below:

(1) Through changes in plasma protein binding and an increase in free fractions of methimazole and MP in the setting of GO: This can be deduced since gluccorticoids (eg, cortisol) are bound to circulating proteins: corticosteroid-binding globulin, α2-globulin, binds about 90% of the circulating hormone and the remainder is free (about 5%–10%) or loosely bound to albumin.[26] MP binds to plasma proteins[27] and does not bind to CBG[28]; methimazole is bound to plasma proteins[29]; thyroid hormones are known to promote albumin catabolism.[30]

(2) CYP450-mediated interaction: Methimazole is metabolized through cytochrome P450 (CYP) enzymes and flavoprotein mixed-function oxidase (FMO)[31] and likely inhibits 2C19, 2C9, 2B6, 3A4 and FMO.[32] Methimazole metabolism through CYP450 (including CYP2A5 enzymes)[33] leads to generation of 2 principal metabolites—N-methylthiourea and glyoxal. N-methylthiourea is considered to be mainly responsible for methimazole-induced hepatotoxicity. Hepatotoxic effects have also been described for sulfenic acid species, the N-methylthiourea oxidization (via FMO enzyme) products.[31] MP is metabolized by CYP3A4[34,35] and is a CYP inducer,[36,37] associated with differential regulation of 20 CYP enzymes (eg, CYP2C13, CYP2D10, and CYP3A2, and CYP2a1 and CYP2a2).[38] MP has been implicated in CYP3A4-mediated drug interactions with CYP3A4 inhibitors itraconazole and ketoconazole previously,[39,40] and inhibitory effects on CYP3A4 of methimazole have been described.[32] The cytochrome P450 (CYP)3A4-mediated drug interaction hypothesis is challenged by a study showing that the use of MP (32 mg once and 8 mg for 9 days) did not result in clinically significant induction of CYP3A4[41]. It should be noted, however, that present case describes the use of MP pulse therapy (doses are far greater than those used in the mentioned study).

(3) Flavin-containing monooxygenases: Another possible explanation may arise from the fact that MP likely up-regulates flavin-containing monooxygenases[42] and that methimazole is an FMO substrate and a competitive inhibitor.[38,43]

In our case, a slight elevation in ALT levels was identified after the fourth MP course with subsequent highest values before the fifth and the sixth MP pulses, when the methimazole dose was 10 mg and then reduced to 5 mg/d before the sixth course and subsequently to 2.5 mg/d due to iatrogenic hypothyrosis. This could have exhibited positive effects on the course of DILI. It is widely accepted that ALT levels greater than 5 times the ULN range suggest a potentially serious process, such as an active liver disease. In this instance, it is appropriate to consider discontinuation of potentially hepatotoxic medications. This case, however, demonstrates that where DILI is caused by the interaction between MP and methimazole, methimazole dose reduction might lead to spontaneous convalescence from liver injury. The fluctuation of transaminases between MP pulses might be positive prognostic signs of reversible course of DILI.

4. Conclusions

Hepatic toxicity is a rare but serious adverse drug reaction of antithyroid drugs and GC. Physicians dealing with thyroid patients should be aware of hepatic toxicity, especially in cases of hyperthyroidism and GO, when methimazole and MP are used concomitantly for an extended period of time, as asymptomatic increases in liver transaminases may occur as result of the interaction between methimazole and MP. The elevation of liver transaminases 5 times above the normal limit suggests discontinuation of hepatotoxic medications such as methimazole and MP. However, in case where no other treatment for the main disease is available, no evidence of autoimmune or viral hepatitis is observed, other liver function tests are normal, and elevations of transaminases fluctuate before and after the pulses, the treatment with MP and methimazole may be continued. If the clinical situation allows, it may be preferable to reduce the methimazole dose. It appears from this case that a significant elevation in liver transaminase levels during the intravenous glucocorticoid and thyrostatic therapy may be reversible if the methimazole dose is slightly reduced and MP treatment continues.

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