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Case Report

Early administration of steroids for the treatment of drug-induced severe liver and renal injury in a patient with hyperthyroidism

Ping Wu[1*], Ping Xu[2*], Xuefeng Ni[3], Xiaohong Jiang[4]

[1]Department of Pharmacology, 3rd Affiliated Hospital, Soochow University, Changzhou, Jiangsu, China; [2]Department of Key Laboratory of Infection and Immunity, 5rd Affiliated Hospital, Soochow University, Suzhou, Jiangsu, China; [3]Department of Tumor, 3rd Affiliated Hospital, Soochow University, Changzhou, Jiangsu, China; [4]Department of Endocrinology, 3rd Affiliated Hospital, Soochow University, Changzhou, Jiangsu, China. [*]Equal contributors.

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Abstract: Acute hepatic and renal failure rarely occur simultaneously. Our case is to report the effect of early methylprednisolone treatment on these patients. We describe the clinical presentation, course, and outcome of a 61-year-old man patient with hyperthyroidism, who was treated with methimazole but developed an allergic reaction to the antithyroid drugs that led to pruritus and cholestatic hepatic injury, acute renal injury was found at the same time. Then, suspectible drugs were stopped; methylprednisolone and other symptomatic drugs were given. To monitor the patient's condition in real time, renal and liver functions were also detected closely. Results: This patient's renal and liver functions were nearly normal with immediate discontinuation of suspectible drugs and timely administration of methylprednisolone. Our case showed that methylprednisolone could be a possible additional way of treatment for cases with drug-injured severe liver and renal function patients.

Keywords: Methimazole, cholestatic liver injury, acute renal failure, methylprednisolone

Introduction

Oral methimazole is an effective treatment of hyperthyroidism and has been used for more than 50 years [1]. Since its introduction into clinical practice, several reports of hepatic dysfunction related to methimazole have been published [2]. The etiologies of methimazole-induced hepatotoxicity include allergic and drug-induced liver injuries, autoimmune/systemic disease, and idiopathic disease. The extent of liver injury ranges from mild to severe, but delayed diagnosis and treatment can result in unpredictable outcomes, including fatal liver injury.

It was also reported that drug-induced acute kidney injury occurs in approximately 20% of patients, especially in critically ill patients [3]. Acute kidney injury is characterized by acute tubular necrosis, acute interstitial nephritis (AIN), or severe necrotizing vasculitis [4]. AIN is responsible for up to 3% of all cases of acute kidney injury, and is considered to be a non-dose-dependent idiosyncratic reaction [5, 6]. Although AIN may develop within several hours or months after starting the responsible agent, about 80% of patients with AIN show renal symptoms within 3 weeks. Along with the clinical manifestations of AIN, patients may also present with low-grade fever, eosinophilia, maculopapular rash, and mild arthralgia [7].

Several reports have described the successful use of steroids to treat methimazole-induced hepatotoxicity [8]. By contrast, very few reports have described the efficacy of administering steroids to treat drug-related renal failure and there are no randomized controlled trials in this setting, although the reports to date have shown positive effects in some patients [9].

Simultaneous liver hepatotoxicity and renal failure is very rare. Here, we report an extremely rare case of a patient with Graves' disease who developed methimazole induced-hepatotoxicity

Table 1. Renal function tests

Date	05/16/13	5/17/13	5/21/13	5/24/13	5/27/13	5/29/13	5/31/13	6/8/13
BUN (mmol/L)	10.85	10.69	12.59	11.31	14.52	13.62	12.18	9.82
Cre (μmol/L)	216.2	214.2	198.8	89.3	134.9	102.3	101.2	97.9
UA (μmol/L)	341.8	336.4	318.6	264.5	325.4	305.0	305.8	235.3

BUN blood urea nitrogen (normal range 1.70-8.30 mmol/L), Cre creatinine (normal range 44.0-144.0 mmol/L), UA uric acid (normal range 90.0-450.0 μmol/L).

Table 2. Liver function tests

Date	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	γ-GTP (IU/L)	TB (μmol/L)	DB (μmol/L)	IB (μmol/L)
05/16/13	62	21	469	732	58.7	47.3	11.4
05/17/13	55	18	682	667	65.6	48.0	17.6
05/21/13	39	13	420	556	66.9	49.7	17.2
05/27/13	39	12	369	459	36.8	28.2	8.6
05/31/13	32	10	298	355	28.0	20.8	7.2
06/04/13	29	11	238	269	20.5	15.4	5.1
06/08/13	26	11	203	214	14.3	11.9	2.4

ALT alanine aminotransferase (normal range 7-40 IU/L), AST aspartate aminotransferase (normal range 13-35 IU/L), ALP alkaline phosphatase (normal range 50-135 IU/L), γ-GTP γ-glutamyl transpeptidase (normal range 7-45 IU/L), TB total bilirubin (normal range 4.0-19.0 μmol/L), DB direct bilirubin (normal range 1.5-7.0 μmol/L), IB indirect bilirubin (normal range 2.0-15.0 μmol/L).

and allergic renal damage. To our knowledge, this is the first case of this kind. This was successfully treated with steroids following combined therapy with drugs to treat specific symptoms.

Case report

A 61-year-old man was referred to our hospital with a 6-week history of fatigue, weight loss of 8 kg, and tachycardia. He was diagnosed with hyperthyroidism on April 16, 2013, and was prescribed methimazole (10 mg twice daily). His liver and renal function tests and white blood cell count were within normal ranges before starting antithyroid therapy. However, after about 22 days of treatment with methimazole, the patient complained of pruritus. At an outpatient clinic, he was prescribed anti-allergic drugs for 2 days, which improved his symptoms. However, 1 week later, he was referred to our clinic again because of dark urine, jaundiced sclerae, pharyngalgia, and low-grade fever. Liver function tests revealed the following: aspartate aminotransferase, 62 IU/L (normal range 13-35 IU/L); alanine aminotransferase, 39 IU/L (normal range 7-40 IU/L); alkaline phosphatase, 732 IU/L (normal range 50-135 IU/L); total bilirubin, 58.7 μmol/L (normal range 4.0-19.0 μmol/L); and serum creatinine, 216.2 μmol/L (normal range 44.0-144.0 mmol/L). Based on these findings, the patient's liver and renal function was impaired and was hospitalized. His urine volume was normal and no edema was apparent in his legs.

His medical history revealed that he was allergic to penicillin and gentamicin. He reported that he had been diagnosed with hypertension 6 years earlier and had been treated with indapamide. Two months before the present admission, he was switched to 80 mg valsartan once daily. He did not smoke or drink alcohol. Before the administration of methimazole, his liver and renal function was in the normal range. After hospitalization, biochemical tests revealed the following: thyroid stimulating hormone, <0.01 μIU/mL (0.30-5.00 μIU/mL); free triiodothyronine, 10.33 pmol/L (normal range 2.10-5.40 pmol/L); free tetraiodothyronine, 32.37 pmol/L (normal range 9.00-25.00 pmol/L); thyroid hormone receptor antibody, 18.32 IU/L (normal range 0.00-12.00 IU/mL); thyroid peroxidase anti-body, 126.50 IU/mL (normal range 0.00-12.00 IU/mL); and anti-thyroid microsome antibody, 87.37 IU/mL (normal range 0.00-50.00 IU/mL). These findings were consistent with the diagnosis of hyperthyroidism. Hematology tests revealed the following: white blood cell count, 6.29×10^9/L (normal range $3.50\text{-}9.50 \times 10^9$/L);

red blood cell count, 3.35 × 10^{12}/L (normal range 4.00-5.50 × 10^{12}/L); neutrophil count, 2.93 × 10^9/L (normal range 2.00-7.00 × 10^9/L); and eosinophilic granulocytes 1.43 × 10^9/L (normal range 0-0.50 × 10^9/L). The patient's renal function data are summarized in **Table 1**, and liver function data are summarized in **Table 2**. His urinary protein, albumin, and white blood cell count were normal. Tumor markers were normal and hepatitis A, B, and C serological studies were negative, as were tests for antibodies against cell nuclei, mitochondria, and smooth muscle. The patient's blood pressure is in the normal range during the period of the whole hospitalization.

Because we considered that the patient's liver damage was caused by methimazole, we deemed it necessary to stop methimazole. Valsartan was also stopped since the patient's impaired hepatic and renal functions. We also prescribed the patient with ursodeoxycholic acid, methionine adenosyltransferase, magnesium isoglycyrrhizinate, and versicolor polysaccharopeptide to repair liver damage. The patient was also given a combination of α-ketoacid and acetyl carbon to treat his renal injury. Because there were no improvements in liver or kidney function after 8 days of treatment with this regimen, we added oral prednisone (8 mg three times daily). His serum creatinine level decreased to the normal range within 5 days of treatment with prednisone (**Table 1**). Total bilirubin and other liver biochemical parameters also decreased gradually towards the normal range within 18 days of treatment (**Table 2**). The patient was prescribed methylprednisolone 8 mg tid after discharge from hospital and the dose was tapered off within 2 months. The patient is a candidate for radioactive iodine ablation of the thyroid gland to treat his hyperthyroidism.

Discussion

Acute hepatic and renal failure are severe clinical conditions and may occur as adverse drug reactions. Pruritus and hepatotoxicity are the most common complications in patients prescribed methimazole; the incidence of methimazole-induced hepatotoxicity ranges from 0.1% to 0.2% [10]. The patient's high blood bilirubin is related to elevated direct bilirubin, which is responsible for cholestatic jaundice, a known adverse drug reaction of methimazole. The patient's Council for International Organizations of Medical Sciences liver damage scale score was 9, and the causal relationship for methimazole-induced cholestatic liver injury was classified as highly probable.

Drug induced renal injury always includes two types: pre-renal failure and intrinsic renal failure. Since the patient's blood pressure is in the normal range during the whole hospitalization, and there is no other hemodynamic instability performance, we can exclude pre-renal failure from experience. We believe it was probably induced by valsartan in our patient for the following reasons. First, the patient had no history or recent risk factors for renal disease. Second, there was a clear temporal relationship between the initiation of valsartan and methimazole, and the emergence of renal and liver injury. Third, although angiotensin II receptor antagonists can lead to acute renal failure, and are often associated with nephrotoxicity [11], AIN is a rare side effect of these kinds of drugs. While labels of its similar kind drugs, angiotension converting enzyme inhibitors, such as lisinopril, has indicated that it may cause AIN during early administration time. Another hypothesis is that, because valsartan is mostly excreted in bile, the serum valsartan concentration may increase in cholestatic jaundice, and might contribute to the emergence of renal failure. Of course, methimazole induced AIN could not be excluded absolutely although there is no related report so far, our patient's renal injury is just more likely caused by valsartan speculated from our clinical experience. Re-administration of valsartan or methimazole was not performed because the patient had other severe side effects, especially hepatic damage, and we felt that it would be unethical.

Our patient's urinary protein, albumin, white blood cell count, and red blood cell count were within normal ranges; only his blood eosinophil count was elevated at the time of admission (1.43 × 10^9/L), and he presented with low-grade fever at the same time. Tests for anti-neutrophil cytoplasmic antibodies and other immune system disease markers were all negative. Unfortunately, our patient refused to undergo renal biopsy for diagnostic confirmation; therefore, the diagnosis was based on his fever, eosinophilia, urinary tests, and acute renal fail-

ure, which were consistent with drug-induced AIN.

Early diagnosis of drug-induced hepatotoxicity or acute renal failure and prompt discontinuation of the suspected causative drugs are essential components of its management. Methimazole-associated hepatotoxicity might involve autoimmune-like hepatitis, which is responsive to corticosteroid therapy [8]. Although there is controversy about the use of steroids in the treatment of drug-induced AIN, some investigators have reported that renal function recovers rapidly and completely in patients given steroids within 2 weeks of discontinuing the causative drugs. Others, however, have failed to confirm this possibility.

In our patient, we discontinued methimazole and valsartan, and administered methylprednisolone (8 mg three times daily) 1 week later, and tapered it within 2 months. The patient's renal creatinine level returned to the normal range within 1 week of starting methylprednisolone. His liver function also gradually returned to normal. Although it is unclear whether these improvements are because of steroid therapy and/or discontinuing the causative drugs, administration of a steroid had a successful outcome in our patient.

Conclusion

Briefly, Simultaneous acute hepatic injury and renal failure is a serious but rare condition in patients with hyperthyroidism, Administration of glucocorticoid may have good outcomes in such patients. Meanwhile, whether methimazole or valsartan may induce AIN need to be researched in future, and physicians should carefully use drugs excreted in bile because of the risk of hepatic injury in patients with hyperthyroidism.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Xiaohong Jiang, Department of Endocrinology, The Third Affiliated Hospital, Soochow University, 185 Juqian Road, Changzhou 213003, Jiangsu Province, China. Tel: 0086 519 68870000; Fax: 0086 68870000; E-mail: gwhglyy@163.com

References

[1] Wu X, Liu H, Zhu X, Shen J, Shi Y, Liu Z, Gu M and Song Z. Efficacy and safety of methimazole ointment for patients with hyperthyroidism. Environ Toxicol Pharmacol 2013; 36: 1109-1112.

[2] Memi E, Karras S, Tzotzas T and Krassas GE. Propylthiouracil hepatitis: report of a case and extensive review of the literature. J Pediatr Endocrinol Metab 2012; 25: 331-343.

[3] Bentley ML, Corwin HL and Dasta J. Drug-induced acute kidney injury in the critically ill adult: recognition and prevention strategies. Crit Care Med 2010; 38: S169-174.

[4] Perico N and Remuzzi G. Acute kidney injury: more awareness needed, globally. Lancet 2015; 386: 1425-1427.

[5] Krishnan N and Perazella MA. Drug-induced acute interstitial nephritis: pathology, pathogenesis, and treatment. Iran J Kidney Dis 2015; 9: 3-13.

[6] Galesic K, Prkacin I, Tisljar M, Horvatic I and Ljubanovic DG. [Drug induced allergic interstitial nephritis]. Lijec Vjesn 2011; 133: 276-283.

[7] Raghavan R and Eknoyan G. Acute interstitial nephritis - a reappraisal and update. Clin Nephrol 2014; 82: 149-162.

[8] Karkhanis J, Verna EC, Chang MS, Stravitz RT, Schilsky M, Lee WM and Brown RS Jr. Steroid use in acute liver failure. Hepatology 2014; 59: 612-621.

[9] Raza MN, Hadid M, Keen CE, Bingham C and Salmon AH. Acute tubulointerstitial nephritis, treatment with steroid and impact on renal outcomes. Nephrology (Carlton) 2012; 17: 748-753.

[10] Livadas S, Xyrafis X, Economou F, Boutzios G, Christou M, Zerva A, Karachalios A, Palioura H, Palimeri S and Diamanti-Kandarakis E. Liver failure due to antithyroid drugs: report of a case and literature review. Endocrine 2010; 38: 24-28.

[11] Howse MLP and Bell GM. Drugs and toxins that damage the kidney. Medicine 2011; 39: 356-361.