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Methimazole-Induced Acute Kidney Injury During the Initial Treatment for Graves' Disease: A Rare Case Report and Literature Review

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Abstract: As a commonly used oral drug for the treatment of hyperthyroidism, methimazole has common adverse reactions, such as a granulocytopenia, thrombocytopenia, arthralgia, skin allergy, etc. The reports of kidney injury caused by methimazole are rare, and the clinical understanding is insufficient, so it is easy to misdiagnosis. This paper reports a middle-aged male patient who was diagnosed with hyperthyroidism in our hospital and developed acute kidney disease after treatment with methimazole. Creatinine and kidney injury-related protein levels decreased after treatment with methimazole. After the primary disease was excluded, acute kidney injury caused by methimazole was highly suspected. The aim of this paper is to improve the safety of methimazole and reduce the rate of missed diagnosis and misdiagnosis.

Keywords: Hyperthyroidism; Methimazole; Adverse drug reactions; Acute kidney injury

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1. Introduction

Graves' disease (GD) with a prevalence of 0.56% is an autoimmune thyroid disease and the most common cause of hyperthyroidism in China Methimazole (MMI), a thionamide drug that blocks the synthesis of thyroid hormones, is recommended by the Chinese Society of Endocrinology (CSE) as the preferred option for the initial treatment of Graves' disease [1, 2]. Although effective, the adverse effects of MMI can vary from mild side effects including skin rash, gastrointestinal upset, and arthralgias to severe side effects such as agranulocytosis, toxic hepatitis, and vasculitis [3]. However, there are few reports of MMI-induced nephrotoxicity.

Acute kidney injury (AKI) is a common clinical syndrome that is characterized by a sudden deterioration of renal function. According to the Kidney Disease Improving Global Outcomes (KDIGO) criteria, AKI is diagnosed when serum creatinine level (SCr) increases by 0.3 mg/dL (or ≥ 26.5 μmol/L) within 48h, or rises to ≥ 1.5-fold from

baseline within the prior 7 days and/or a decrease in urine output(UO) < 0.5 mL/kg/h for 6–12 h [4]. Approximately 1 in 5 hospitalized patients and 1 in 2 patients admitted to the intensive care unit (ICU) experience AKI [5–7]. The incidence of AKI in outpatient is estimated between 1.4 and 3.0% [8, 9]. AKI can be caused by a multitude of reasons, which include ischemia/reperfusion injury, sepsis, low cardiac output, disrupted autoregulation, and exposure to nephrotoxic agents [10]. Medications have been reported to contribute 14%–26% to the episodes of AKI in prospective cohort studies and 37.5% in a cross-sectional survey [7, 11, 12]. Herein, we present a rare case of AKI in a man with Graves' Disease after initiation of MMI.

2. Case report

A 41-year-old man visited our department complaining of palpitations and hand tremors for a month. No fever or other symptoms were present. His body weight remained unchanged. He had no past medical history and family history of note. Physical examination showed a heart rate of 96 per minute, respiratory rate 16 per minute, blood pressure of 136/67 mmHg, and temperature 36.8°C. The thyroid gland was grade 2 diffusely enlarged but not tender. There were fine tremors on his hands when outstretched and his eyes were normal. The rest of the clinical examination was unremarkable.

Thyroid ultrasound revealed diffuse thyroid enlargement along with an increased vascular flow. No nodules were identified. Laboratory results revealed a normal complete blood cell count, hepatic enzymes, and renal function with baseline Scr 78 μmol/L. Thyroid function test were notable for thyroid-stimulating hormone (TSH) < 0.001 mIU/L (0.56–5.91 mIU/L), free thyroxine (FT4) 47.11 pmol/L (7.64–16.03pmol/L), free triiodothyronine(FT3) 12.37pmol/L, (3.28–6.47pmol/L), antithyroglobulin antibodies 2.8 IU/mL (TPOAb, normal < 40 IU/mL), antithyroid peroxidase antibodies 0.2 IU/mL (TgAb, normal < 40 IU/mL) and TSH receptor antibody 3.1U/L (TRAb, normal < 1.75 IU/mL).

A diagnosis of Graves' hyperthyroidism was made. He was started with a daily dose of 30mg methimazole along with sustained-release metoprolol 47.5mg once daily. He was subsequently followed monthly in the outpatient clinic. One month later, his TSH improved to 0.132 mIU/L, free FT4 decreased to 4.75 ng/dL, and TT3 decreased to 3.7 ng/dL. Renal function tests were not checked at that time. He continued to take methimazole. Two months after thiamazole initiation, renal function tests were checked, and Scr level was elevated to124μmol/L. Repeat labs in one month showed persistently elevated Scr of 119 μmol/L. He was admitted to the nephrology ward for further evaluation. Renal ultrasonography revealed normal size and echogenicity of both kidneys. Laboratory testing showed complete resolution of thyroid function. The 24-h urine total protein was slightly high at 0.25g (normal: 0.02~0.15 g). The levels of alpha-1 microglobulin, N-acetyl-β-Dglucosaminidase, β2-microglobulin, and retinol binding protein in the urine were increased (18.4mg/24h U/L, 20U/L, 0.24mg/L, and 2.5mg/L, respectively). Negative results were found upon testing for antineutrophil cytoplasmic autoantibodies (ANCA), myeloperoxidase (MPO) antibodies, and proteinase 3 (PR3) antibodies. Levels of complement factors C3 and C4 were normal. Tests for HIV and hepatitis B and C virus were negative. Due to concern for drug-induced AKI and a normalization of thyroid function, methimazole was discontinued. Urinalysis 2 weeks after methimazole discontinuation revealed that alpha-1 microglobulin and β2-microglobulin returned to the normal range. The patient was then discharged and regularly followed up. A biopsy was not performed.

At the four-month follow-up after discharge, his Scr recovered to 106μmol/L, and 24-h urine total protein returned to 0.02g/24h. Six months after discharge, his Scr was 96 μmol/L. However, he was experiencing

palpitations again and laboratory values showed a relapse of Graves' disease with significantly reduced TSH of < 0.005mIU/mL, elevated free T4 of 49.35 pmol/L, and elevated free T3 of 10.53pmol/L. After refusing the radioiodine therapy, thyroid surgery, and conversion to propylthiouracil, he was rechallenged with methimazole 10mg daily. On a subsequent outpatient visit two weeks after methimazole rechallenge, the level of Scr was elevated to 103 μmol/L. He continued to take 10mg of methimazole daily and gradually reduced the dose. After 12 months of treatment, the thyroid function was completely restored, and the drug was discontinued. The patient continued to be followed up and monitored for renal function in the endocrinology clinic. His serum creatinine returned to the baseline level 18 months after the drug was discontinued.

3. Discussions

Methimazole has unique advantages over propylthiouracil in regard to better adherence, more rapid improvement in serum concentrations of thyroxine and triiodothyronine, and lower risk of liver function damage and vasculitis. Minor adverse effects such as pruritic rash, arthralgia, and gastrointestinal upset occur in approximately 5% of patients receiving methimazole [13]. The major adverse effects include agranulocytosis, hepatotoxicity, and anti-neutrophil cytoplasmic antibody–positive vasculitis typically begin within the first few weeks of starting therapy [14]. Other rare side effects such as hypoglycemia, pancreatitis, aplastic anemia, and lupus erythematosus have also been reported in the literature. Kidney damage caused by methimazole is rare, with few clinical reports, and this adverse effect is not mentioned in the existing instructions for use of the drug.

Kidney injury caused by methimazole can be manifested as nephrotic syndrome and AKI. We described a middle-aged male patient who was diagnosed as hyperthyroidism due to "head tremor". Within two months after the start of treatment with methimazole, the patient presented with only a slight increase in urinary protein without nephrotic syndromes such as edema and hypoproteinemia. In the absence of other renal toxins, his serum creatinine (SCr) rose to 1.6 times higher than baseline. The increase in serum creatinine was consistent with the definition of AKI as defined by Kidney Disease Improvement Global Outcomes (KDIGO). The onset time increased and decreased significantly with the withdrawal of methimazole, which further confirmed that methimazole induced kidney injury.

Review of the published literature revealed 3 case reports detailing the association of methimazole with the development of nephrotoxicity. Shell *et al.* have reported a case of methimazole-induced AKI in a 72-year-old male patient [15]. After taking Propylthiouracil for 5 years, the patient was adjusted to methimazole treatment due to the excessive dosage of Propylthiouracil and poor medication compliance, and kidney injury occurred 1 month later. Scr levels increased 1.6-fold from baseline, and renal function returned to normal 2 weeks after methimazole withdrawal. Reynolds *et al.* reported a 20-year-old male with no previous history of nephropathy who developed renal dysfunction after using methimazole for 1 month [16]. Edema, massive proteinuria (urinary protein quantity 7g/24h), and hypoproteinemia (serum albumin 11g/L) were associated with the complex signs of renal disease. Renal function recovered after 2 weeks of disuse, and urinary protein level decreased significantly. The pathological results were highly similar to those of animal toxic nephropathy caused by aminonucleoside of purinamycin.

Zheng *et al.* reported a 30-year-old male who was treated for hyperthyroidism with methimazole and developed facial and lower limb edema, accompanied by proteinuria (urinary protein quantification 2.86 g/24 h) and hypoproteinemia (serum albumin 31.6 g/L) two months later [17]. The pathological outcome was membranous

renal disease. Twenty-four hours after stopping methimazole, the urinary protein quantity decreased to 1.1g. After routine treatment with glucocorticoids and cyclophosphamide, the urinary protein level decreased to normal, edema completely subsided, and clinical cure was achieved. The cases reported by Reynold *et al.* were similar to those reported by this study's research group, both of which were consistent with kidney injury caused by methimazole, but the clinical manifestations were more severe and the renal pathology examinations were perfected [16]. The patient reported in this case refused to undergo renal pathological examination and could not determine the pathological classification of AKI, but the urine renal function examination showed significant increases in urinary n-acetyl-D-glucosamine and urinary retinol-binding protein, indicating that methimazole induced renal tubule injury.

In recent years, the cases of methimazole-induced severe connective tissue diseases have increased year by year, which may be due to the rising incidence of Graves' disease and the increase in the number of people taking methimazole drugs, which has also increased the academic attention to methimazole. Anca-associated vasculitis is a rare but serious adverse event that can also involve the kidneys and is characterized by acute kidney injury, but kidney injury is more secondary to lupus erythematosus and small vasculitis, and is associated with anti-neutrophil cytoplasmic antibodies. In this case, immune-related nephropathy was ruled out because the antinuclear antibody spectrum, ANCA, and immunoglobulin were not abnormal.

Acute kidney injury (AKI) is a clinically significant event of rapid decline in renal function, with a variety of causes, but usually grouped into one of three broad categories: prerenal, intrinsic, and postrenal. Prerenal AKI is a response to renal hypoperfusion, often in the setting of hypovolemia or reduced cardiac output. Postrenal AKI results from urinary tract obstruction. Intrinsic AKI is the product of cellular injury within the kidney, with prolonged ischemia and nephrotoxic agents playing major roles. The pathophysiology of AKI is a complex interplay of pathways triggered by an inciting event, which leads to an imbalance of oxygen supply and demand. At present, some scholars believe that the mechanism of AKI may be related to the following aspects: haemodynamic instability, microcirculatory dysfunction, tubular cell injury, tubular obstruction, renal congestion, microvascular thrombi, endothelial dysfunction, and inflammation [17].

Renal recovery after AKI is a complex process that is not entirely understood, though it appears to be dependent on AKI severity, aetiology, duration, and baseline renal function [18]. Older age, lower baseline kidney function, longer duration of AKI, and higher severity of AKI contribute to maladaptive repair [19]. The timeline and trajectory of renal recovery will depend on reversal of the pathophysiological processes involved [19]. In addition, there is no clear conclusion whether there is a racial difference in kidney recovery after kidney injury, and some studies have shown that blacks and Hispanics are associated with incomplete kidney recovery after AKI [20].

In the past, it was generally believed that with the gradual recovery of the structure and function of renal tubular epithelial cells after AKI, the renal function of most patients could also be completely recovered, and the possibility of developing chronic kidney disease and end-stage renal disease was very low [21]. However, in recent years, a large number of studies have shown that AKI is closely related to the occurrence and development of CKD [22]. A significant number of patients with AKI, even with partial or complete recovery of kidney function, may still progress to CKD and even ESRD. It has been reported that about 20% of AKI patients will develop CKD after 3 years [23]. AKI is currently considered to be an independent risk factor for CKD [24]. The number of episodes of AKI, severity, and presence of underlying kidney disease were associated with progression to CKD. The mechanism by which AKI transitions to CKD is complex and not fully understood, It is mediated by various mechanisms, including renal tubular epithelial cell repair disorder and cell cycle arrest, endothelial cell injury

and microcirculation vascular bed reduction, chronic inflammatory response, mitochondrial dysfunction, renin-angiotensin system activation, epigenetic changes, tissue and cell aging, etc., which can eventually lead to or aggravate renal fibrosis and cause CKD. A similar condition to this is described in a case report published by Rajesh that depicts the condition of a 46-year-old married woman who was treated with Carbimazole for her hyperthyroidism, and following which, she developed AKI and gradually progressed to chronic kidney disease (CKD) [25]. The patient described here, within 19 months of stopping methimazole in July 2022, the eGFR level fluctuated between 65.3 and 80.2mL/ (min·1.73m2) under dynamic monitoring. The patient did not develop chronic kidney disease at present; the eGFR didn't recover to baseline, and further follow-up is required.

At present, there is no specific drug to prevent AKI, and prevention strategies emphasize more on the identification and risk assessment of high-risk groups, avoiding triggers, and dynamic monitoring, to detect AKI early and manage it. However, there is no consensus on the duration, frequency, and content of follow-up, which can be based on the individual risk of patients (previous history of CKD, proteinuria, diabetes, or organ failure); AKI severity during hospitalization; The recovery of renal function at discharge was determined. Recognition of the early signs of tubular injury utilizing sensitive biomarkers may also hold future promise to predict early kidney injury and allow cessation of potential nephrotoxins [26]. Follow-up should include diet, health guidance, patient-specific avoidance of nephrotoxins, post-discharge medication adjustment, and assessment of renal function (Scr, GFR, and proteinuria).

Therefore, in clinical use of methimazole, attention should be paid to the urine volume, urine routine, edema and other conditions of patients, such as suspected kidney injury, Scr, urine protein and other related tests should be improved, after the primary disease is excluded, the possibility of kidney injury caused by methimazole should be vigilant, the rate of missed diagnosis and misdiagnosis should be reduced, and the kidney pathology examination should be improved to identify the cause if necessary.

4. Conclusion

Although methimazole is a widely used antithyroid drug, its potential to induce acute kidney injury (AKI) remains underrecognized in clinical practice. This case highlights methimazole-associated AKI in a middle-aged male with hyperthyroidism, evidenced by elevated creatinine and kidney injury markers that improved upon drug discontinuation. Given the rarity of reported renal complications, clinicians should maintain heightened vigilance for this adverse effect to ensure timely diagnosis and intervention. Enhanced awareness of methimazole's nephrotoxic potential is crucial to improving medication safety and reducing rates of missed or misdiagnosed cases. Routine renal monitoring in patients receiving methimazole therapy may be warranted.

Disclosure statement

The authors declare no conflict of interest.

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