Methimazole overdosing and hypothyroidism treatment, an explanation for prolonged emergence from anesthesia

Nathan DuBois MD, Michael Lin MD, Ali Eldouh MD, Elizabeth Rivas MD

Abstract

A 60-year-old woman with a past medical history of Graves' disease, heart failure with reduced ejection fraction, and type 2 diabetes mellitus underwent an intramedullary fixation of the left hip. Postoperatively, the patient was transferred to the postoperative anesthesia care unit and later the surgical intensive care unit due to concern for hemodynamic instability. While in the SICU, the patient had altered mentation and continued to have altered mental status for the next six days. Neurologic etiologies were ruled out, and no other causes were identified. Her mentation only began to improve after withholding methimazole and starting levothyroxine. Days after her mentation returned to baseline, the patient was successfully discharged to an inpatient rehab facility. An explanation for her altered mental status due to hypothyroidism, induced by methimazole, is explored in this case report.

Keywords: Graves' disease, methimazole, hypothyroidism, delayed emergence

Introduction

Methimazole is an antithyroid medication used in the treatment of hyperthyroidism, such as Graves' disease.[1] This drug inhibits the enzyme thyroid peroxidase o that iodination cannot occur to form triiodothyronine (T3) and thyroxine (T4). An appropriate dose of methimazole (ranging from 5 mg to 40 mg daily) can help patients achieve a euthyroid state, but an inappropriate dose can induce a hypothyroid state. In the perioperative setting, alterations in thyroid levels can cause complications with anesthesia and recovery. Hypothyroidism has multisystem effects including decreased spontaneous minute ventilation, reduced plasma volume, hyponatremia and impaired hepatic drug metabolism, all of which can increase the risk of delayed return in consciousness after anesthesia.[2] Hypothyroidism is also associated with altered mental status. It can present as decreased attention, concentration, psychomotor function, and executive function. Other factors that can propagate changes in mentation include decreased cerebral blood flow and glucose metabolism. In a patient who is being treated for hyperthyroidism and presents with altered mental status days after surgery, it would be beneficial to assess for and treat hypothyroidism as a possible cause.

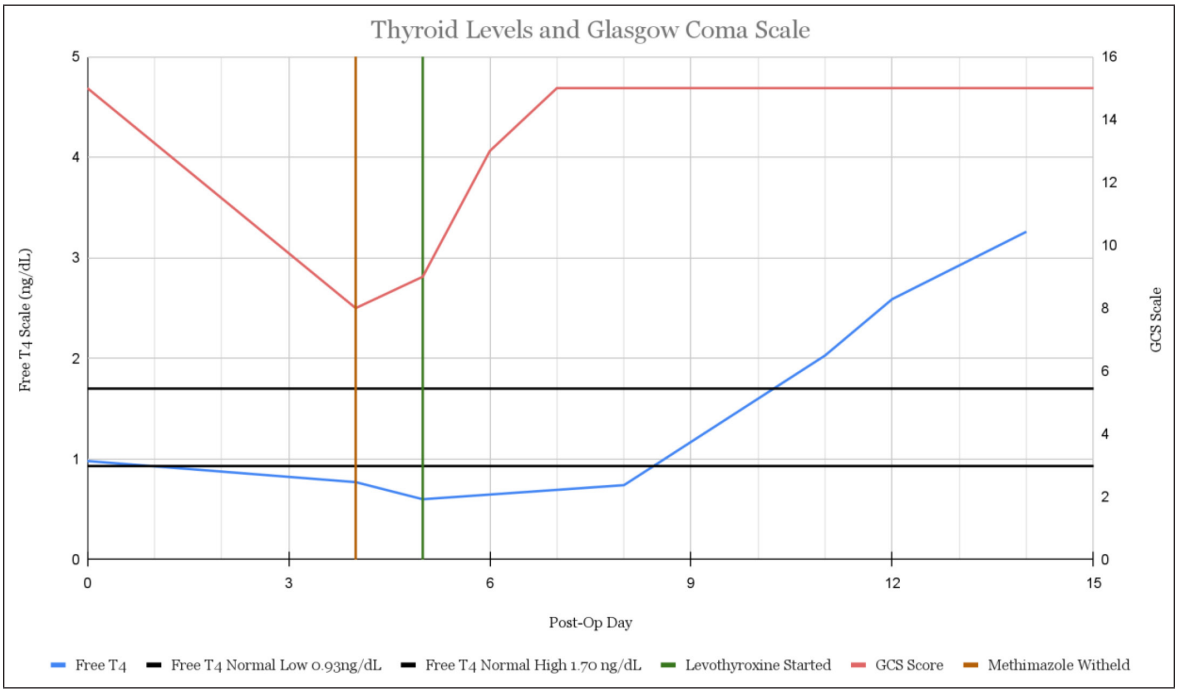
Corresponding author: **Nathan DuBois**
Contact Information: Nathan.Dubois@ttuhsc.edu
DOI: 10.12746/swjm.v13i56.1495

Case

A 60-year-old woman with a past medical history of Graves' disease treated with methimazole 10 mg once daily, type 2 diabetes mellitus, hypertension, and heart failure with reduced ejection fraction underwent intramedullary fixation of the left hip after sustaining a ground level fall. Her previous surgical history was unremarkable for any surgical or anesthetic complications. Her lab values were all normal except for a TSH of less than 0.01 mcIntUnit/ml. Preoperatively, the patient was considered alert and oriented.

During the surgical procedure, the patient required blood transfusion and norepinephrine drip to maintain adequate perfusion. After the surgery, the patient was extubated to a non-rebreather mask, and remained on

Table 1. Patient's Thyroid Levels versus Glasgow Coma Scale



norepinephrine infusion. Postoperatively, the patient was drowsy. Given the concern for hemodynamic instability, the patient was admitted to the surgical intensive care unit for further postoperative management.

On postoperative day (POD) 1 she was noted to have an acute kidney injury likely from hypoperfusion, and later started on continuous renal replacement therapy (CRRT). She continued to have altered mentation, arousable only to sternal rub.

On POD 2 her mental status remained unchanged. Small infarcts in the bilateral watershed areas between the anterior and medial cerebral arteries were discovered. However, these abnormalities did not completely explain her poor responsiveness.

By POD 3, the patient was able to localize pain, but was non-verbal. On POD 4, thyroxine levels were found to be decreased (Table 1), so methimazole was held on POD 4 and IV levothyroxine 100 mcg was started on POD 5. On POD 6 the patient was able to follow simple commands. Her creatinine returned to baseline and CRRT was stopped. By POD 7 mentation had improved significantly, and the patient was considered alert and oriented with return to baseline on POD 8. Given her overall improvement, she was later transferred to the floor, awaiting placement for inpatient rehab.

Discussion

This was a complex case that did not have an explicit explanation for her extended period of altered mental status lasting 6 days. Based on her responsiveness to treatments, we hypothesized that low free T4 levels from methimazole could attributed in her altered mental status.

While 6 days of altered mental status is clinically unique, a possible explanation lies within the patient's treatment for hyperthyroidism with methimazole. In patients who are in a hypothyroid state, the plasma half-life of methimazole can increase by approximately 20%.[3] Therefore, an explanation of why our patient continued to have decreasing thyroid levels can be understood as a compounding effect. A decrease in thyroxine levels could precipitate a mild hypothyroid state. This mild hypothyroid state could then increase the plasma half-life of methimazole, thus increasing its plasma concentration. This increased concentration would further decrease FT4 levels, further exacerbating the hypothyroid state.

Evidence for this compounding effect is anecdotally supported by the fact that the patient's improved mentation coincided with withholding methimazole and further improvement was achieved after the administration of levothyroxine.

Furthermore, hypothyroidism and reduce the expression of the NADPH cytochrome P450 reductase enzyme in mice (up to 85% reduction). This enzyme has an important role in the electron transfer to CYP enzymes. This is significant because methimazole is metabolized primarily through the CYP1A2 and CYP2C9 enzymes.[5] Decreased CYP enzyme activity slows down the metabolism of methimazole which can increase its plasma concentration. This relationship between hypothyroidism, decreased activity of NADPH cytochrome p450 and decreased CYP enzyme activity and decreased methimazole metabolism can further explain why the patient had decreased thyroid levels for multiple days.

It is worth noting that methimazole is metabolized mostly by the liver, but not entirely. Approximately 10–15% of an administered dose is excreted, unmetabolized, in the urine.[5] Considering the onset of acute kidney injury in this case report, this could be another contributing factor for decreased methimazole clearance and subsequently increased methimazole plasma concentration.

Conclusion

This case offers an explanation for a patient who had altered mental status for six days status post intramedullary fixation of the left hip. Altered mental status induced by relative hypothyroidism caused by increased methimazole plasma concentration, decreased hepatic metabolism, and decreased renal excretion likely contributed to the patients' persistent condition. This hypothesis is further supported by the timing of improved mental status by withholding methimazole and initiating levothyroxine. This case report demonstrates the importance of judicious medication review, especially in patients presenting with altered mental status from hypothyroidism induced methimazole.

Article citation: DuBois N, Lin A, Eldouh M, Rivas E. Methimazole overdosing and hypothyroidism treatment, an explanation for prolonged emergence from anesthesia. The Southwest Journal of Medicine 2025; 13(56):53–55
From: Texas Tech University Health Sciences Center, School of Medicine (NB); (Department of Anesthesia (AL, ME, ER), Texas Tech University Health Sciences Center, Lubbock, Texas
Submitted: 6/9/2025
Accepted: 6/29/2025
Conflicts of interest: none

References

1. Cooper DS. Antithyroid drugs. N Engl J Med 2005 Mar 3; 352(9):905–17. doi: 10.1056/NEJMra042972.
2. Thomas E, Martin F, Pollard B. Delayed recovery of consciousness after general anaesthesia. BJA Educ 2020 May; 20(5):173–9. doi: 10.1016/j.bjae.2020.01.007.
3. Vesell ES, Shapiro JR, Passananti T, et al. Altered plasma half-lives of antipyrine, propylthiouracil, and methimazole in thyroid dysfunction. Clin Pharmacol Ther 1975 Jan;17(1):48–56. doi: 10.1002/cpt197517148.
4. Ram PA, Waxman DJ. Thyroid hormone stimulation of NADPH P450 reductase expression in liver and extrahepatic tissues. Regulation by multiple mechanisms. J Biol Chem 1992 Feb 15;267(5):3294–301. doi: 10.1016/s0021-9258(19)50730-x.
5. Awosika AO, Singh G, Correa R. Methimazole. [Updated 2023 Sep 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan.–Sept. 2023.