Lithium as Pre-radioablative Treatment of Graves' Disease Complicated by Thyroid Storm and Methimazole-induced Agranulocytosis: A Case Report

Valerie R. Ramiro, MD,[1] Jose Paolo P. Panuda, MD,[2] Cecileen Anne M. Tuazon, MD,[1] Roland Reuben B. Angeles, MD,[1] and Iris Thiele Isip-Tan, MD[2]

Case Summary

Thyroid storm and thionamide-induced agranulocytosis are both rare and serious medical emergencies. We report a case of a patient in which these two rare events simultaneously occurred. A 33-year-old male, maintained on Methimazole for Graves' Disease, presented with fever, throat pain, and uncontrolled thyrotoxic symptoms. Methimazole was promptly discontinued. Thyroid storm was alternatively treated with lithium, hydrocortisone, and propranolol. Agranulocytosis was managed supportively with GCSF and empiric antibiotics. Lithium was maintained until after radioablation. When thionamides are contraindicated, lithium is a viable option for the acute management of thyroid storm and a bridge to definitive therapy.

Introduction

A thyroid storm is a rare, life-threatening endocrinological emergency due to a severe exacerbation of hyperthyroid symptoms, often with multi-organ involvement. Acute illnesses, infections, surgery, radioactive iodine (RAI) therapy, and discontinuation of antithyroid medications are some of the known precipitants of thyroid storm.[1] Although thyrotoxicosis of any etiology may progress to thyroid storm, Graves' Disease is the most common.[2] Based on the 2012 nationwide study by the Philippine Society of Endocrinology and Metabolism (PSEM), the prevalence of thyroid function abnormalities in the Philippines is 8.53%, with subclinical thyroid disease comprising the majority. Overt hyperthyroidism was found in only 0.61% of the population.[3] There is no data on the overall prevalence of thyroid storm in the Philippines. Still, of 431 patients admitted to our institution for hyperthyroidism from 2016 to 2017, there have been 23 reported cases of thyroid storm.

In treating hyperthyroidism, inhibition of thyroid hormone synthesis using thionamides, such as methimazole and propylthiouracil (PTU), is indispensable. Similarly, in the acute management of thyroid storm, immediate administration of thionamides, preferably PTU due to its faster onset of action and additional inhibition of the peripheral conversion of thyroxine to triiodothyronine, at higher and more frequent doses is essential.[1,2]

Thionamides are generally well-tolerated, and side effects are commonly mild (e.g., urticaria, rash, arthralgias). Of the serious side effects, the most feared is agranulocytosis, which is a rare, idiosyncratic adverse drug reaction that occurs abruptly and usually within the first three months of therapy. [4,5] When a serious drug reaction occurs due to the intake of one thionamide, switching to another thionamide is not advised due to the risk of cross-reactivity, as high as 50%.[6]

This then poses a dilemma in circumstances wherein the cornerstone of treatment is contraindicated, and alternatives are limited and unconventional and with narrow safety profiles. Therefore, this case aims to demonstrate the successful use of lithium as an alternative treatment option when thioamides, the mainstay of therapy for thyroid storm, are unsuitable.

Case Presentation

A 33-year-old Filipino male was diagnosed with diffuse toxic goiter five months prior to admission. Outpatient work-up showed a diffusely enlarged thyroid gland with no nodules nor calcifications on thyroid ultrasonography

[1] Department of Medicine, University of the Philippines – Philippine General Hospital
[2] Section of Endocrinology, Department of Medicine, University of the Philippines – Philippine General Hospital
Corresponding Author: Dr. Valerie R. Ramiro, Email: vrramiro@yahoo.com

Table I: The patient's Burch-Wartofsky score* on initial presentation at the Emergency Room.

Parameter	Patient's Presentation	Points
Temperature	38^0c	30
Central Nervous System Effects	Absent	0
Gastrointestinal-Hepatic Dysfunction	Jaundice	20
Cardiovascular Dysfunction	110 beats per minute	10
Congestive Heart Failure	Absent	0
Atrial Fibrillation	Chronic	0
Precipitating Event	Present (infection)	10
	TOTAL	70

*A score of 45 or more highly suggests a thyroid storm, a score of 25 to 44 suggests impending storm, while a score less than 25 makes thyroid storm not likely.
From: Burch, H.B. and Wartofsky, L. Life-threatening thyrotoxicosis. Thyroid storm. Endocrinol Metab Clin North Am 1993 22: 263-277.

and increased 24-hour uptake of radioactive iodine on a thyroid scan. In addition, atrial fibrillation was documented on the electrocardiogram (ECG). He was maintained on Methimazole 40 mg daily and Propanolol to control hyperthyroid symptoms.

He presented with a 2-week history of fever, throat pain, and difficulty swallowing at our emergency room. There was no associated cough, rashes, or gastrointestinal complaints. Three days prior to admission, fever and dysphagia worsened and were now accompanied by epigastric pain, non-mucoid, non-bloody, watery diarrhea, easy fatigability, restlessness, difficulty in concentration, and palpitations. The persistence of symptoms prompted the patient to seek admission at our institution.

The patient was normotensive, tachycardic on initial physical examination with a heart rate of 110 beats per minute with an irregularly irregular rhythm, febrile (38^{O}C), diaphoretic, and restless. He had icteric sclerae and a uniformly enlarged, doughy, non-tender thyroid gland. On chest examination, breath sounds were clear. Other pertinent examination findings were direct epigastric tenderness and fine fingers tremors. Given the patient's history of diffuse toxic goiter and compatible clinical picture of uncontrolled thyrotoxicosis, an initial assessment of thyroid storm was made based on a Burch-Wartfosky score of 75 (see Table 1). Hence, loading doses of PTU 600 mg, Supersaturated Potassium Iodide (SSKI) 5 drops orally, Hydrocortisone 100 mg IV, and Propranolol 40 mg orally were given.

Laboratory tests done confirmed uncontrolled hyperthyroidism with elevated Free Thyroxine (FT_4) (30.15 pmol/L; Normal range: 9.01-19.05) and Free Triiodothyronine (FT_3) (3.65 pmol/L; Normal range: 2.63-5.7) levels and suppressed Thyroid Stimulating Hormone (0.0018 uIU/ml; Normal range: 0.35-4.94). TSH Receptor Antibody was elevated at >40 UI/L (reference interval: <1.75 UI/L). Liver function tests were abnormal with the following results: aspartate aminotransferase 585 U/L, alanine aminotransferase 1,228 IU/L, Alkaline phosphatase 53 IU/L, and International Normalized Ratio 2.42. The ECG showed atrial fibrillation with a rapid ventricular response, while the chest radiograph was unremarkable. The complete blood count revealed leukopenia (Absolute Neutrophil Count 290 x 10^9/L) and thrombocytopenia (69 x 10^9/L).

On re-examination, the patient's tonsils were inflamed with exudates. Interpreted with a low absolute neutrophil count (ANC) and a history of thionamide intake, the clinical picture was consistent with methimazole-induced agranulocytosis. Subsequent doses of PTU were discontinued, and SSKI was likewise withdrawn. Given that thionamides was the drug class considered the culprit for this patient's agranulocytosis and understandably had to be avoided, the team sought an alternative treatment option, Lithium carbonate 450 mg/tab one tablet given twice daily, to control thyrotoxicosis. Hydrocortisone and propranolol were continued. In addition, he was started on Granulocyte Colony Stimulating Factor (GCSF) 300 mcg SC daily to address the severe neutropenia. Piperacillin-Tazobactam 4.5 g IV every 8 hours was given as empiric broad-spectrum antibiotic coverage for severe sepsis after appropriate cultures were taken. He was admitted to the medical intensive care unit (MICU) for close monitoring.

At the MICU, clinical improvement was observed, and thyrotoxic symptoms gradually diminished. Fever did not recur, and the cardiac rhythm converted to sinus. With the improvement of thyrotoxic symptoms, hydrocortisone was tapered and subsequently discontinued. Serial blood chemistries showed a steady decline in transaminase levels. The ANC reached 6,439 x 10^9/L by the 6th MICU day, and GCSF was discontinued. The patient was transferred to the general ward, where he continued to improve clinically. He was maintained on Lithium 450 mg/tab one tab twice daily. The intravenous antibiotic was shifted to oral Levofloxacin. He was discharged hemodynamically stable and clinically euthyroid.

On outpatient follow-up, the patient had no recurrence of thyrotoxic symptoms and reported no adverse reactions to lithium. Serum lithium concentration taken one week after discharge was 0.70 mmol/L (therapeutic range: 0.6–1.20). Repeat thyroid scan demonstrated bilaterally enlarged thyroid lobes with elevated 2-hour and 24-hour uptake values. An ablative dose of 20 millicuries (mCi) of RAI was administered three weeks after the last doses of PTU and SSKI. Lithium was discontinued five days after RAI therapy. On follow-up after 1 and 2 months, serial FT_4 levels showed a declining trend at 12 pg/ml and 9 pg/ml, respectively (normal range: 11.4 – 23.8), and he remained symptom-free. He was then maintained on low-dose Levothyroxine (50 mcg/day).

Discussion

We were presented with a critical patient who developed methimazole-induced agranulocytosis and thyroid storm at the same time. In this clinical scenario, high-dose thionamides were contraindicated in managing thyroid storm due to agranulocytosis. Agranulocytosis, defined as an absolute granulocyte count less than 500 x 10^9/L, is estimated to occur in 0.37% of patients taking propylthiouracil and 0.35% taking methimazole.[7] It is commonly observed within the first three months of thionamide treatment. Still, it is important to note that it can also occur shortly after thionamides are resumed after a brief discontinuation period of even up to 5 months.[8] In our institution, we only have five recorded cases of thionamide-induced agranulocytosis, all from methimazole, at the time of writing. Other than discontinuation of the culprit drug, treatment is mainly supportive with the administration of GCSF and intravenous broad-spectrum antibiotics.[6,10] GCSF can significantly decrease recovery time and duration of hospital stay among patients with thionamide-induced agranulocytosis.[9,10]

Lithium has long been used as a mood-stabilizing treatment for psychiatric conditions such as bipolar disorder.[11] Lithium, in its 300mg and 450mg tablet formulations, is approved by the Philippine Food and Drug Administration.[12] It is still commonly prescribed by psychiatrists as it is inexpensive compared to the newer drugs for bipolar disorder. Lithium also has utility in the treatment of hyperthyroidism. It can decrease thyroid hormone levels by inhibiting the release of pre-formed thyroid hormone, increasing iodine content within the thyroid gland, and inhibiting the coupling of iodotyrosine residues.[1,13,14]

Several case reports have demonstrated the successful use of lithium as a second-line treatment in Graves' Disease, and thyroid storm.[13,15,16,17] A local case reported by dela Cruz et al. in 2011 reported similar management using lithium carbonate for a patient with thyroid storm and with carbimazole-induced agranulocytosis.[16] Akin and Zheng also presented cases where thionamides were either contraindicated or ineffective, and lithium was used in preparation for definitive therapy, such as radioablation or thyroidectomy.[13,17] Despite marked differences in the lithium dosing regimens used in these case reports, varying from 50 mg daily up to 300 mg thrice a day, lithium levels were monitored closely to maintain therapeutic drug levels in most cases. In our patient, the 450 mg/tab preparation was given one tab twice a day, which amounted to a total of 900 mg lithium per day, similar to the doses used in these previous cases.[13, 15, 16, 17] Lithium also has additional hematologic effects by increasing GCSF and thereby improving neutropenia.[18] In our patient who received both Lithium and GCSF since admission, agranulocytosis resolved on the 6th hospital day.

Physicians rarely use lithium in treating hyperthyroidism because of the fear of possible complications. Common side effects of lithium include weight gain, gastrointestinal upset, polydipsia, polyuria, lassitude, inertia, fine tremors, and acne.[19, 21] In a study by Zheng et al., wherein 51 hyperthyroid patients with antithyroid drug-induced hepatotoxicity and leukopenia received low-dose lithium (50 to 75 mg daily) for 36 weeks, only mild gastrointestinal side effects were reported. These resolved after cessation of the drug.[13] However, serious toxicities rarely develop as long as serum levels do not exceed 1.4 mEq/L.[20] The common side effects aforementioned, which may occur even with lithium plasma levels within the therapeutic range, are fortunately mild and transient. For these cases of mild toxicity, lithium doses can be decreased. The severity of lithium toxicity has a direct correlation with its plasma concentration. Symptoms of moderate toxicity such as hand tremors, confusion, nystagmus, dysarthria, and ataxia will require discontinuation of lithium. Symptoms of severe toxicity such as seizures, syncope, renal failure, coma will necessitate admission to the intensive care unit.[21]

For thyroid storm, Nayak et al. recommend that lithium concentrations be maintained at 0.6 to 1 mmol/L to avoid toxicity and monitor these regularly since lithium levels may change as the patient becomes more euthyroid with the treatment.[14] A case report by Prakash et al. in 2015 showed that even subtherapeutic doses of lithium at 0.5 to 0.6 mmol/L can induce a euthyroid state in Graves' Disease.[15] In our case, the use of lithium at 900 mg per day, with demonstrated lithium serum concentration at 0.70 mmol/L, which is within the therapeutic range, rapidly controlled hyperthyroidism with no side-effects observed.

Besides lithium, other treatment options include steroids, iodine, beta-blockers, plasmapheresis, and cholestyramine.[1,2,14] For our patient, we used hydrocortisone and propranolol, in conjunction with lithium. Unfortunately, cholestyramine was not available during the patient's admission as it is not a widely-marketed drug. Although plasmapheresis was available in our hospital, it was costly, and our patient was already improving with the current medical regimen (i.e., lithium, steroids, and beta-blockers). Likewise, we opted to forego iodine since we planned on imminent RAI as soon as a euthyroid state was achieved.

The 2016 American Thyroid Association guidelines recommend 10 to 15 mCi as RAI treatment for Graves' Disease.[22] For our patient, a higher activity of 20 mCi was used for thyroid ablation. Serial FT_4 determinations after RAI confirmed that the treatment successfully induced a hypothyroid state.

The administration of lithium to our patient effectively treated thyroid storm and served as adequate preparation before radioablation. In the case series by Akin et al., 4 out of the six patients who received adjuvant lithium for 2 to 3 weeks prior to RAI had successful outcomes and did not demonstrate the anticipated post-RAI surge in serum FT_4 and FT_3.[18] One meta-analysis presented consistent but limited evidence that adding lithium to RAI showed a trend towards a higher cure rate

and shorter time to cure compared to RAI alone.[23] This effect is likely due to lithium's ability to increase RAI retention in the thyroid.[24] Hence, lithium may be helpful not only to control hyperthyroidism initially but also to facilitate thyroid ablation with RAI.

Conclusion

In cases when thionamides are contraindicated, lithium is an effective, readily available, and inexpensive option for the acute management of thyroid storm and a bridge to definitive therapy, such as RAI, for Graves' Disease.

Conflict of Interest: None.

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