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Rectal thionamide administration in the setting of thyroid storm: a case report and review of the literature

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Summary

Thyroid storm is a clinical diagnosis characterized by life-threatening multisystemic organ involvement in the setting of uncontrolled hyperthyroidism. Current estimates suggest a mortality rate of up to 30%. Treatment often consists of the administration of thionamide medications, iodine solution(s), corticosteroids, and beta-blockers; in extreme circumstances, both plasmapheresis and thyroidectomy are subsequent therapeutic options. Thionamides are typically administered orally, with the intent of preventing further thyroid hormone synthesis; however, in the literature, there are instances whereby oral access cannot be obtained, and alternative routes of administration are required. We present a case of a patient who presented with a thyroid storm due to lack of adherence to methimazole. During admission, he was found to have significant abdominal pain and ultimately a duodenal perforation requiring strict nil-per-os (NPO) status, due to which he was unable to receive oral thionamides. Due to the lack of availability of intravenous formulations of thionamides in the United States, this patient was treated with an enema compound of propylthiouracil for a total of five per rectum (PR) doses. He would later develop hepatocellular injury, requiring discontinuation and eventual transition to oral methimazole. The literature pertaining to alternative-route thionamide administration is scant, and therefore this case report and literature review is written to provide an up-to-date review and further educate all levels of clinicians about this infrequent (but emergent) situation.

Learning points

- Thyroid storm is a clinical diagnosis for which urgent recognition is required to prevent untoward mortality.
- Treatment for thyroid storm requires prompt administration of thionamides, iodine, corticosteroids, and beta-blockers. In extreme circumstances, treatment considerations include plasmapheresis and thyroidectomy.
- Infrequently, patients with a thyroid storm may not be able to tolerate oral medications, for which alternative routes of access are required.
- Currently, available alternatives include intravenous methimazole (in Europe and Japan), as well as both enema and suppository preparations of propylthiouracil and methimazole.

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Background

First described in 1926 by Lahey as 'the crisis of exophthalmic goiter', thyroid storm (alternatively referred to as a thyrotoxic crisis) is a life-threatening, multisystemic manifestation of hyperthyroidism (1). Systemic involvement includes (but is not limited to) gastrointestinal, cardiovascular, and central nervous system complications. It is estimated that around 1–2% of hospital admissions for thyrotoxicosis are due to a thyroid storm (2). Diagnosis is clinical, with the Burch-Wartofsky scoring system assisting in severity; it should be noted, however, that even with early recognition, the mortality rate can be as high as 30%, with the most common cause of death being multi-organ failure. In the study by Furukawa *et al.* (3), however, their registry study noted a reduction in the mortality rate to 5.5% (compared to 10.9% from other nationwide assessments). A multitude of precipitating factors are responsible for a thyroid storm, which is frequently superimposed in the setting of medication non-compliance (4, 5).

Prompt treatment is necessary for this endocrine emergency. Management is multifactorial and includes the prevention of thyroid hormone production (thionamides, which include propylthiouracil and methimazole), followed by the subsequent prevention of stored thyroid hormone release (via administration of iodine-containing solutions), and blocking the peripheral effects of thyroid hormone (controlled with the administration of a beta-blocker and glucocorticoid). Recent guidelines additionally favor the administration of cholestyramine to enhance the clearance of thyroid hormones by preventing entero-reabsorption. Should the aforementioned interventions be unsuccessful or contraindicated, succeeding treatments include emergent thyroidectomy and/or plasmapheresis (6). Albeit less commonly encountered, instances arise whereby oral access is prevented, and therefore thionamide administration must be administered through alternative routes. While methimazole exists as an intravenous medication, this is not available in the United States; therefore, alternative options include rectal administration of either propylthiouracil or methimazole (7).

We report a case of a thyroid storm in a patient with non-compliance to methimazole, presenting with an acute abdomen with a perforated duodenal ulcer. Oral access was contraindicated, and therefore management included compounding rectal propylthiouracil. Furthermore, we analyze the existing literature pertaining to non-oral thionamide administration.

Case presentation

A 58-year-old gentleman with a one-year history of Graves' disease, diabetes mellitus, cocaine use, hypertension, heart failure, and atrial fibrillation presented to the emergency department with a three-day history of worsening epigastric pain, alongside self-reported melena. He was prescribed methimazole 20 mg as an outpatient but could not recall the last time this medication was taken (nor his carvedilol). There was no recent exposure to iodine or amiodarone administration. Upon presentation, he was afebrile and hemo-dynamically stable but was noted to be tachycardic on the telemetry monitor. He was agitated and complaining of significant diffuse abdominal tenderness.

Investigation

Upon presentation, his thyroid-stimulating hormone was below 0.01 μU/mL and his free T4 (fT4) was 4.03 ng/dL. An electrocardiogram was obtained, demonstrating atrial fibrillation with a rapid ventricular response (heart rate: 152 beats per minute), and physical examination was consistent with diffuse tenderness throughout the abdominal wall. A computed tomography scan was performed, which demonstrated a pneumoperitoneum. Our patient had a Burch-Wartofsky score of 55 (highly suggestive of thyroid storm) and fulfilled the criteria of a definite case following the Japan Thyroid Association diagnostic criteria with severe tachycardia and agitation (8); as a result, endocrinology was urgently consulted. Following the identification of pneumoperitoneum, he was admitted to the medical intensive care unit.

Treatment

The patient was made strictly NPO at the request of the surgical team and had a nasogastric tube placed for decompression. He was subsequently taken to the operating room for a laparotomy (and subsequent Graham patch for a perforated duodenal ulcer). Moreover, he immediately received 200 mg of intravenous hydrocortisone followed by the administration of 50 mg every 8 h, in addition to intravenous metoprolol tartrate of 5 mg. We discussed with our pharmacy, and it was stated that intravenous methimazole was not available in the United States; additionally, intravenous propylthiouracil could not be compounded due to the inability to reach sterilization standards with intravenous formulations. However, the pharmacy was able to conjugate an enema preparation of propylthiouracil. As there was no parenteral alternative to iodine and cholestyramine, these two were omitted from the treatment regimen.

The pharmacy prepared eight tablets of 50 mg in 100 mL of normal saline, producing 400 mg of propylthiouracil (to be administered as a loading dose enema). The patient was subsequently prescribed 250 mg of propylthiouracil (enema) every 4–6 h, receiving a total of five doses of the enema preparation of propylthiouracil. However, the patient began to develop

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Table 1 Trend of liver enzymes and thyroid hormone profile following thionamide administration.

Day	AST, IU/L	ALT, IU/L	ALP, IU/L	TBR, mg/dL	fT4, ng/dL	TSH, µU/mL	TT3, ng/dL
April 22nd - PR PTU Started	35	45	133	3.8	4.03	< 0.01	N/A
April 23rd	1256	590	95	4.6	N/A	N/A	N/A
April 24th – PTU Discontinued	N/A	N/A	N/A	N/A	N/A	N/A	N/A
April 25th	403	511	86	4.1	1.58	N/A	78.35
April 26th	131	301	71	4	N/A	N/A	N/A
April 27th – Oral MTZ Started	84	247	74	5.4	N/A	N/A	N/A
April 28th	54	91	79	4.5	N/A	N/A	N/A
April 29th	39	139	75	4	1.14	0.02	48.32

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; fT4, free T4; MTZ, methimazole; PR, per rectum; PTU, propylthiouracil; T. Bili, total bilirubin; TSH, thyroid-stimulating hormone; TT3, total T3.

a hepatocellular injury pattern likely believed to be secondary to the medication, for which it was stopped (Table 1). At 48 h, a repeat thyroid function test was performed, with an improvement in fT4 to 1.58 ng/dL and a total T3 (TT3) of 78.35 ng/dL. Whilst the hepatocellular injury rapidly improved upon discontinuation of propylthiouracil, the patient was not tolerating anything orally, and the pharmacy was unable to prepare methimazole suppositories. As a result, he did not receive any further thionamide medications for another four days. However, during this time, he was managed with a weaning dosage of intravenous hydrocortisone to 50 mg daily. Four days later, following surgical clearance for diet and oral medications (at which point his liver enzymes had normalized), he was resumed on his home dosage of 20 mg methimazole.

Outcome and follow-up

Following the resumption of oral methimazole, a repeat thyroid function panel demonstrated a TSH of 0.02 µU/mL, an fT4 of 1.14 ng/dL, and a TT3 of 48.62 ng/dL. There was a transient elevation of his liver enzymes, which normalized rapidly while continuing the medication. He had developed sarcopenia during admission due to limited mobility, for which he had been recommended to be discharged to a skilled nursing facility; however, he left against medical advice after eleven days of hospitalization.

Discussion

Thionamides – including methimazole, propylthiouracil, and in Europe carbimazole – are the cornerstone of treatment for hyperthyroidism, and indeed a thyroid storm, which are administered orally and function to inhibit further thyroid hormone synthesis. Infrequently, however, oral access may be compromised, requiring alternative routes of delivery. While intravenous methimazole is available in Europe and Japan, this is not available in the United States, and therefore, alternatives include both enema and suppository propylthiouracil, as well as suppository methimazole (Table 2). Methimazole is available as

Table 2 Propylthiouracil and methimazole alternative routes for administration.

Route	Propylthiouracil	Methimazole
Suppository		
	200 mg are dissolved into a polyethylene glycol base, which is subsequently placed in suppository tablets.	1200 mg are dissolved in 12 mL of water, followed by the addition of 52 mL of cocoa butter (which contains two drops of polysorbate (Span) 80). The mixture is stirred, forming an emulsion, which is then placed in 2.6 mL suppository molds and allowed to cool.
Retention Enema*		
	Option 1. Between eight and twelve 50 mg tablets are dissolved in 90 mL of water (sterile). Option 2. Eight 50 mg tablets are dissolved in 60 mL of either mineral oil enema or in 60 mL of sodium-phosphate enema solution.	
- Intravenous		Not available in the United States

Adapted from Malhotra & Bhadada (5).
*For either option, this is followed by Foley catheter insertion into the rectum with balloon inflation to prevent leakage (achieving 2-h retention).
mL, millilitres; mg, milligrams.

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an intravenous solution (in Europe and Japan) due to its freely soluble neutral aqueous solutions; no such formulation currently exists for propylthiouracil due to it being insoluble at physiologic pH (7). Moreover, as described in our case report, propylthiouracil could not reach sterilization standards to be formulated into an intravenous solution. As depicted by Kerrigan *et al.* (9), transdermal thionamides have been studied in animals, but no topical formulation has demonstrated efficacy in human subjects (albeit topical methimazole is used for hyperpigmented facial lesions).

While the American Thyroid Association does not mention non-oral formulations of thionamides, this is briefly mentioned in the Japanese guidelines, advising the usage of intravenous methimazole in patients who are severely ill and have a disturbance in consciousness (6, 10). Alfadhli *et al.* (7) provide a pathway (Fig. 1) demonstrating the inclusion of non-oral thionamide administration in the algorithm for the management of a thyroid storm when oral access is compromised.

Our case report demonstrates a unique situation whereby oral thionamide administration was not feasible; this has been infrequently reported in the literature (Table 3). Only a handful of cases in the literature have been reported with a presentation similar to ours involving a perforated bowel (11, 12, 13, 14). While a nasogastric tube was inserted for decompression in our patient, Lee *et al.* (12), advocate against the blind insertion of a nasogastric tube to prevent worsening of the perforation and state that in such settings PR thionamide is preferred.

Jongjaroenprasert *et al.* (15) studied the comparison of propylthiouracil enema versus suppository in 15 newly diagnosed hyperthyroid subjects, demonstrating greater bioavailability with the enema preparation (however, they state that both are comparably efficacious). One caveat to the enema, however, is the concern for leakage. Therefore, as demonstrated by Yeung *et al.* (14), a Foley catheter is typically inserted into the rectum, followed by clamping of the catheter and balloon inflation to allow retention for 2 h (this was not performed in our patient). Jongjaroenprasert *et al.* (15) furthermore state that suppositories are more feasible for the nursing staff, are less likely to cause leakage, and are likely to be more comfortable for patients. Walter & Bartle (16), however, state that rectal absorption is likely to be more efficacious over suppositories due to the greater surface area for contact. While oral propylthiouracil can produce a bitter oral taste (limiting adherence), peculiarly, Jongjaroenprasert *et al.* (15) note that in four subjects, within 5–10 min of rectal administration, this similar phenomenon appeared, suggesting dysgeusia is likely a systemic (rather than local) effect.

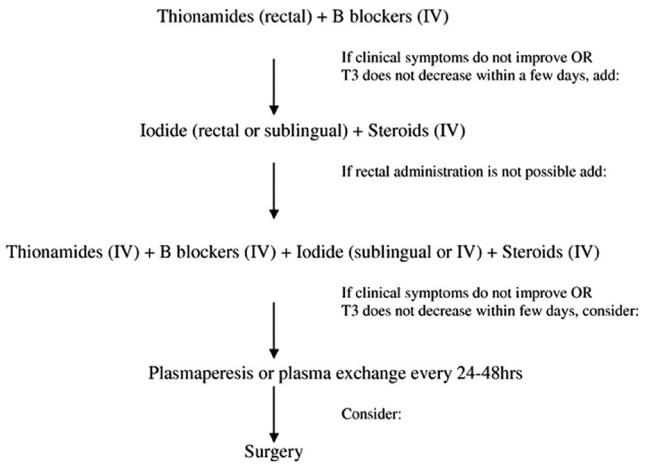

Figure 1

Obtained with permission from Alfadhli *et al.* (7).

Apart from the discomfort to the patient, other possible reasons for avoiding PR administration of thionamides are the concern for poorer absorption and efficacy. Of note, however, in certain situations, even if oral access is possible, rectal administration may be preferred; Wiggins *et al.* (13) present a case of a thyroid storm leading to vasodilatory shock requiring vasopressors. The authors suggest that in a thyroid storm (and consequential vasodilatory shock), oral absorption might be impaired while on vasopressors, suggesting that rectal administration may be more beneficial.

In six euthyroid subjects, Nabil *et al.* (17) compared the administration of 60 mg of oral to suppository methimazole, stating there is no significant difference between the rate of absorption or peak plasma levels between either route, suggesting that the factors controlling oral absorption are in part similar to rectal absorption at the same dosage (time to peak: 0.5 h, peak level: 1.12 ± 0.21 µg/mL). Bartle *et al.* (18) further studied seven euthyroid subjects, receiving two differing formulations of 400 mg propylthiouracil suppository (diethanolamine or Witepsol H 15), noting lower bioavailability with rectal (compared to oral) administration (peak levels: oral = 7.12 ± 0.48 µg/mL; diethanolamine: 1.2 ± 0.31 µg/mL; Witepsol H 15: 2.30 ± 0.35 µg/mL) and a slightly longer time to peak (oral: 1.99 ± 0.26 h; diethanolamine: 4.72 ± 0.96 h; Witepsol H 15: 2.0 ± 0.35 h). Walter & Bartle (16) furthermore note the lower absorption of 400 mg rectal compared to oral propylthiouracil in a patient with a thyroid storm using Fleet's mineral oil followed by Fleet's phosphor-soda, achieving a peak level of 3 µg/mL and a time to peak of 3 h; as noted by van Hoogdalem *et al.* (19) both of these have laxative properties, which could be a confounder and suggest aqueous solutions could perhaps result in better absorptive profiles. It is for this reason that Jongjaroenprasert *et al.* (15) chose water as a vehicle for enema administration. Jongjaroenprasert *et al.* (15) studied 15 subjects with hyperthyroidism, who received either propylthiouracil in the form of a water enema or suppository in polyethylene glycol, to directly compare the pharmacokinetics between the two formulations. As noted by the authors, the water-suspension enema appeared to be faster absorbed with early time to peak

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Table 3 Review of the literature describing pharmacokinetic properties of rectal administration of thionamides.

				Pharmacokinetic parameters		
Reference	**Subjects, *n***	**Thyroid status**	**Drug/preparation**	**Peak level, µg/mL**	**Time to peak, h**	**Half life**
Walter & Bartle (16)	1	Thyroid storm	PTU 400 mg (Fleet phosphor-soda enema)	3	3	
Zweig *et al.* (20)†	1	Hyperthyroid	PTU 400 mg (suppository)	~6.8	3	82 min
Zamora *et al*. (11)	1	Hyperthyroid	Methimazole 20 mg PR twice daily (formulation unknown)	N/A		
Lee *et al*. (12)	1	Thyroid storm	PTU 400 mg (enema)	N/A		
Wiggins *et al*. (13)	1	Thyroid storm	PR PTU (dose and formulation unknown)	N/A		
Nabil *et al*. (17)	6	Euthyroid	Methimazole 60 mg (suppository)	1.12 ± 0.21	0.5	
Bartle *et al.* (18)	7	Euthyroid	Group 1: PTU 400 mg (suppository, diethanolamine)	1.2 ± 0.31	4.72 ± 0.96	
			Group 2: PTU 400 mg (suppository, Witepsol H 15)	2.30 ± 0.35	2 ± 0.35	
Yeung *et al.* (14)	1	Thyroid storm	PTU 250 mg (water enema)	N/A		
Cansler *et al.* (21)	1	Hyperthyroid	PTU 400 mg (Fleet enema)	1.9	1	
Jongjaroenprasert *et al*. (15)	15	Hyperthyroid	Group 1: PTU 400 mg (water enema)	3.89 ± 0.34	1.43 ± 0.2	1.13 ± 0.12 h
			Group 2: PTU 200 mg × 2 (400 mg) (suppository in polyethylene glycol)	2.01 ± 0.38	2.88 ± 0.44	N/5A
Letham *et al*. (22)	2	Hyperthyroid	PTU 200 mg PR (formulation unknown)	N/A		
			PTU PR (dose/formulation unknown)			
Maung *et al.* (23)	1	Thyroid storm	PTU 400 mg (Fleet enema) loading dose, followed by 200 mg (Fleet enema)	N/A		
Baik *et al.* (24)	1	Thyroid storm	PTU 400 mg (enema)	N/A		

Adapted from Jongjaroenprasert *et al.* (15).
†Other pharmacological parameters included: volume of distribution = 0.4 L/kg; bioavailability = 68%; clearance = 137 mL/min; average concentration at steady state = 5.5 ng/mL.
N/A, not applicable, PR, per rectum, PTU, propylthiouracil

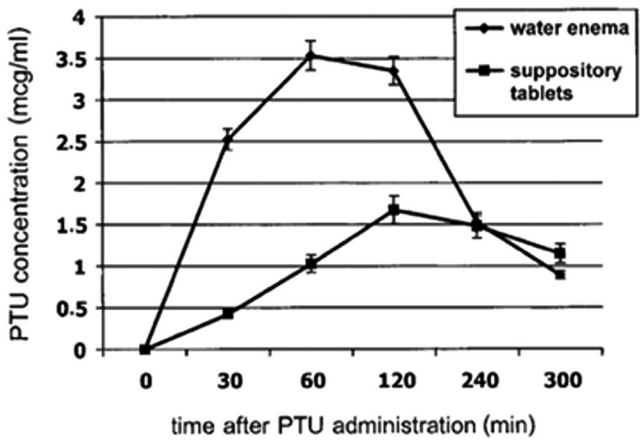

Figure 2

Obtained with permission from Jongjaroenprasert *et al.* (20). PTU, Propylthiouracil.

levels (1.43 ± 0.2 h vs 2.88 ± 0.44 h, respectively), as well as greater peak concentrations (3.89 ± 0.24 µg/mL vs 2.01 ± 0.38 µg/mL, respectively) (Fig. 2).

Zweig *et al.* (20) present a case similar to ours with a perforation and thyroid storm, whereby the patient required initial PR propylthiouracil 400 mg suppository, calculating a peak level of 6.8 µg/mL and a time to peak of 3 h. The authors subsequently transitioned the patient to oral propylthiouracil and provided a direct comparison of the pharmacokinetics between the two formulations (Table 4). Zweig *et al.* (20) furthermore suggest that rectal administration bypasses the first-pass metabolism in the liver (33% of oral antithyroid medications are metabolized in the liver), with the caveat of risking mucosal irritation. Cansler *et al.* (21) note in their case report of a patient with concurrent duodenal obstruction and thyroid storm calculating a peak level of 12.9 µg/mL and a time to peak of 1 h with the administration of 400 mg of propylthiouracil (Fleet enema). Similar reports in a patient with concurrent thyroid storm and bowel obstruction were reported by

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Table 4 Direct comparison of pharmacokinetic preparations of oral and rectal propylthiouracil.

Variable	**Oral** (200 mg every 8 h)	**Suppository** (400 mg every 6 h)
Average plasma concentration*	1.9 ng/mL	5.5 ng/mL
Clearance	165 mL/min	137 mL/min
Half-life	68 min	82 min
Bioavailability	75%	68%
Volume of distribution	0.4 L/kg	0.4 L/kg

Adapted from Zweig *et al.* (20).
*at steady state.

Yeung *et al.* (14), measuring a peak level of 12.9 µg/mL and a time to peak of 1.5 h.

A further area of uncertainty likely to represent hesitancy to prescribe PR thionamides is the effect itself upon thyroid hormone synthesis; a literature review of the evidence available is demonstrated in Table 5. While Bartle *et al.* (18) noted poorer peak levels and time to peak with rectal administration of propylthiouracil, the authors note a near-similar increase in serum reverse T3 levels (rT3) (oral: rT3 increase of 25%, $P < 0.05$; diethanolamine: rT3 increase of 20%, $P < 0.05$; Witepsol H 15: rT3 increase 16%, $P < 0.05$). Unlike the study by Bartle *et al.* (18) which was performed on euthyroid subjects, Jongjaroenprasert *et al.* (15) assess the inhibitory response in hyperthyroid subjects, noting a significant decrease in free T3 (decrease of 21.48% compared to 28.41%, respectively), and a significant increase in rT3 in both the water propylthiouracil enema and suppository groups (increase of 77% compared to 29.6%, respectively). While Jongjaroenprasert *et al.* (15) fail to demonstrate a clinically significant alteration in free T4 levels (decrease of 5% compared to 18%, respectively), the authors suggest that this is likely to be explained by the long half-life of thyroxine (in comparison to tri-iodothyronine), stating that thionamides require uptake in the thyroid gland for at least 8 h prior to demonstrating any effect; as the authors only measured for up to 300 min, this likely

Table 5 Review of the literature describing thyroid hormone alterations following administration of rectal thionamides.

				Outcome			
Reference	**Subjects, *n***	**Thyroid Status**	**Drug/preparation**	**fT3**	**fT4**	**T4**	**rT3**
Walter & Bartle (16)	1	Thyroid storm	PTU 400 mg (Fleet phosphor-soda enema)		↓68.7%	↓68.8	
Zweig *et al.* (20)	1	Hyperthyroid	PTU 400 mg (suppository)		↓55.4%		
Zamora *et al*. (11)	1	Hyperthyroid	Methimazole 20 mg PR twice daily (formulation unknown)		↓54.4%		
Lee *et al*. (12)	1	Thyroid storm	PTU 400 mg (enema)	↓74%	↓69.2%		
Wiggins *et al*. (13)	1	Thyroid storm	PR PTU (dose and formulation unknown)				
Nabil *et al*. (17)	6	Euthyroid	Methimazole 60 mg (suppository)				
Bartle *et al.* (18)	7	Euthyroid	Group 1: PTU 400 mg (suppository, diethanolamine)				↑20%
			Group 2: PTU 400 mg (suppository, Witepsol H 15)				
Yeung *et al.* (14)	1	Thyroid storm	PTU 250 mg (water enema)		↓55.6%		
Cansler *et al.* (21)	1	Hyperthyroid	PTU 400 mg (Fleet enema)			↓22.3%	
Jongjaroenprasert *et al*. (15)	15	Hyperthyroid	Group 1: PTU 400 mg (water enema)	↓21.48%	↓5%		↑77%
			Group 2: PTU 200mg × 2 (400 mg) (suppository in polyethylene glycol)	↓28.41%	↓18%		↑29.6%
Letham *et al*. (22)	2	Hyperthyroid	PTU 200 mg PR (formulation unknown)		↓36.1%*		
			PTU PR (dose/formulation unknown)				
Maung *et al.* (23)	1	Thyroid storm	PTU 400 mg (Fleet enema) loading dose, followed by 200 mg (Fleet enema)	↓66%	↓82.2%		
Baik *et al.* (24)	1	Thyroid storm	PTU 400 mg (enema)	↓87.2%	↓17.4%	↓78.7%‡	

Adapted from Jongjaroenprasert *et al.* (15)
*Only described in the first subject; ‡value is for total T4; ↓, decrease of; ↑, increase of.
fT4, free thyroxine, fT3, free triiodothyronine, PTU, propylthiouracil, PR, per rectum, TT3, total triiodothyronine; rT3, reverse T3.

explains why this study, as opposed to our case report and that of others, demonstrates clinically significant reductions in thyroid hormone levels (Table 5).

Conclusion

In summary, thyroid storm is a clinical diagnosis that, if missed, poses a significant risk of mortality. Thionamides (propylthiouracil and methimazole), which serve to prevent further thyroid hormone synthesis, are paramount in management. Administration is oral; however, when alternative routes of access are required, both rectal (propylthiouracil and methimazole) and intravenous (methimazole) options are available and have demonstrated efficacy and safety. While current guidance does not provide recommendations for non-oral access in the management of hyperthyroidism, perhaps this should be reviewed and incorporated into prospective guidelines.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the study reported.

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Patient consent
A consent form was signed by the patient prior to the submission of the case report.

Author contribution statement
MB, CC were the residents involved in the care of the patient, SS was the Endocrine fellow, and AR was the attending Endocrinologist involved in the case. MB, CC, SS, and AR wrote the manuscript together as well as the literature review. The draft was revised and finalized by MB.

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