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Review Article

Acute and emergency care for thyrotoxicosis and thyroid storm

Alzamani Mohammad Idrose

Emergency Department, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

Thyroid hormones affect all organ systems and, in excess, can cause increased metabolic rate, heart rate, ventricle contractility, and gastrointestinal motility as well as muscle and central nervous system excitability. Thyroid storm is the extreme manifestation of thyrotoxicosis with an estimated incidence of 0.20 per 100,000 per year among hospitalized patients in Japan. The mortality of thyroid storm without treatment ranges from 80% to 100%; but with treatment, the mortality rate is between 10% and 50%. The diagnostic strategy for thyroid storm may take into consideration Burch–Wartofsky scoring or Akamizu's diagnostic criteria. Multiple treatment aims need to be addressed in managing thyroid storm effectively. This paper puts together all aspects to be considered for the management of hyperthyroidism and thyroid storm during the acute and emergency phase as well as consideration of special populations.

Key words: Acute, emergency, hyperthyroidism, thyroid storm, thyrotoxicosis

INTRODUCTION

ALL ORGAN SYSTEMS are affected by thyroid hormones. Thyroid hormones increase metabolic rate, heart rate, and ventricle contractility, as well as muscle and central nervous system (CNS) excitability. Two major types of thyroid hormones are thyroxine (T4) and triiodothyronine (T3), released in the ratio of 20:1, respectively. Peripherally, T4 is converted to the active T3, which is three to four times more potent than T4.

Hyperthyroidism is a state of excess circulating thyroid hormone resulting only from intrinsic thyroid gland hyperfunction, whereas *thyrotoxicosis* refers to excess circulating thyroid hormone originating from any cause (including thyroid hormone overdose).

The extreme manifestation of thyrotoxicosis is thyroid storm, which manifests as an acute, severe, life-threatening hypermetabolic state caused either by excessive release of thyroid hormones, causing adrenergic hyperactivity, or altered peripheral response to thyroid hormone following the presence of one or more precipitants.

Corresponding: Alzamani Mohammad Idrose, MBBS, MMed (Emergency), MITM, MSc, BoJ, Emergency Department, Hospital Kuala Lumpur, Kuala Lumpur 50586, Malaysia. E-mail: alzamani@yahoo.com.

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EPIDEMIOLOGY

THE INCIDENCE OF thyroid storm in hospitalized patients in Japan is estimated to be 0.20 per 100,000 per year with more than 10% mortality.[1] In the USA, the overall incidence of hyperthyroidism is estimated to be between 0.05% and 1.3%, with the majority of cases being subclinical in terms of presentation.[2] Among hospitalized thyrotoxicosis patients, the incidence of thyroid storm has been noted to be <10%.[3] The mortality of thyroid storm without treatment ranges between 80% and 100%; with treatment, this figure is between 10% and 50%. Multiple organ failure was reported to be the most common cause of death in thyroid storm, followed by congestive heart failure, respiratory failure, arrhythmia, disseminated intravascular coagulation, gastrointestinal perforation, hypoxic brain syndrome, and sepsis.[1] The mortality rate in the group with a total bilirubin level >3 mg/dL is significantly higher.[1]

CAUSES OF HYPERTHYROIDISM OR THYROTOXICOSIS

HYPERTHYROIDISM CAN BE due to thyroid gland problems or endocrinal axis problems known as primary and secondary causes respectively. It can also be due to exogenous pathology or drug induction.

Primary and secondary hyperthyroidism

Primary hyperthyroidism is caused by the excessive production of thyroid hormones from the thyroid glands. Secondary hyperthyroidism is caused by the excessive production of thyroid-releasing hormones or thyroid-stimulating hormones (TSHs) in the hypothalamus and pituitary, respectively.

In the case of thyroid storm, the most common underlying cause of hyperthyroidism is Graves' disease. It is caused by the thyrotropin receptor antibodies that stimulate excessive and uncontrolled thyroidal synthesis and secretion of thyroid hormones. It occurs most frequently in young women (10 times more common in women compared to men) at any age group.[4]

Toxic multinodular goiter is the second most common group in which thyroid storm tend to occur. Rare causes of thyrotoxicosis leading to thyroid storm include hypersecretory thyroid carcinoma and thyrotropin-secreting pituitary adenoma.

Exogenous and drug-induced causes of thyrotoxicosis

Exogenous causes include non-thyroidal diseases caused by production of thyroid hormones at sites away from the thyroid glands like ectopic thyroid tissue or metastatic thyroid carcinoma. Excessive thyroid hormone ingestion either by intentional or accidental intake may bring about thyrotoxicosis. Struma ovarii, an ectopic thyroid tissue, is a rare form of teratoma that produces thyroid hormones. Metastatic thyroid cancer and human chorionic gonadotropin-secreting hydatidiform mole are other rare extrinsic causes of thyrotoxicosis. Drug-induced thyrotoxicosis is caused by the interaction of thyroid gland with certain drugs, for example, α-interferon, interleukin-2, or amiodarone causing stimulation of thyroid hormone production.

PATHOPHYSIOLOGY

WHEN THERE IS an excess of thyroid hormones, circulating T4 and T3 are taken into the cytoplasm of cells. T4 is converted to its active form, T3, by 5′-deiodinase enzyme through deiodination in the outer ring of the T4 molecule. Within the cytoplasm, T3 then exerts its effect by passing into the nucleus and binding to thyroid hormone receptors or thyroid hormone-responsive elements to induce gene activation and transcription.[5] The receptors receiving the hormone stimulate changes specific to the tissue.

Lipogenesis and lipolysis occur as thyroid hormone induces enzymes early in the lipogenic pathway, including malic enzyme, glucose-6-phosphate dehydrogenase, and fatty acid synthetase. Increased cholesterol production occurs through transcription of 3-hydroxy-3-methylglutaryl coenzyme A reductase. Nevertheless, thyroid hormones also cause increased excretion of cholesterol in the bile, generally resulting in a decrease in total cholesterol. In the pituitary gland, thyroid hormones exert negative regulation on the transcription of genes for the subunit of TSH, resulting in suppressed TSH in the context of thyrotoxicosis.

During thyroid storm, precipitants such as infection, stress, myocardial infarction, or trauma will multiply the effect of thyroid hormones by the freeing of thyroid hormones from their binding sites or increased sensitivity of the receptors in tissues through increases in target cell adrenergic receptor density or postreceptor modifications in signaling pathways.

THYROID STORM PRECIPITATION

THE MOST COMMON precipitating cause of thyroid storm is infection.[6] Other causes include diabetic ketoacidosis, hypoglycemia, hyperosmolar coma, pulmonary embolism, thyroid hormone overdose, withdrawal of antithyroid medications, iodinated contrast medium ingestion, vascular accidents, surgery, stress, parturition, eclampsia, trauma, and myocardial infarct. In some patients undergoing radioactive iodine therapy for hyperthyroidism, thyroid storm may ironically occur following treatment due to withdrawal of antithyroid drugs, release of thyroid hormones from damaged thyroid follicles, or the effect of radioactive iodine itself. In approximately 20–25% of cases, no acute precipitant is identified.

Clinical features

History and comorbidities

Patients with thyrotoxicosis may present with constitutional symptoms such as generalized weakness and fatigue. Heat intolerance, diaphoresis, fever, voracious appetite but poor weight gain, anxiety, emotional lability, palpitations, diarrhea, and hair loss are common historical features. Medications that can precipitate thyrotoxicosis include iodine-containing medications, including radiographic contrast material, amiodarone, or large doses of topical povidone–iodine (especially if there is skin break). Amiodarone has iodine-rich benzfuran content that increases the level of iodine upon intake. If there is a history of hyperthyroidism, treatment and patient's compliance with medication should be determined.

Physical examination

The signs and symptoms of hyperthyroidism are shown in Table 1. Fever is often present in thyroid storm and may be quite high. It may herald the onset of thyrotoxic crisis in previously uncomplicated disease. Palpitations, tachycardia, and dyspnea are common. A pleuropericardial rub may be

Table 1. Symptoms and signs of thyrotoxicosis

Affected system	Symptoms	Signs
Constitutional	Lethargy Weakness Heat intolerance	Diaphoresis Fever Weight loss
Neuropsychiatric	Emotional lability Anxiety Confusion Coma Psychosis	Fine tremor Muscle wasting Hyperreflexia Periodic paralysis
Ophthalmologic	Diplopia Eye irritation	Lid lag Dry eyes Exophthalmos Ophthalmoplegia Conjunctival infection
Endocrine: thyroid gland	Neck fullness Tenderness	Thyroid enlargement Bruit
Cardiorespiratory	Dyspnea Palpitations Chest pain	Widened pulse pressure Systolic hypertension Sinus tachycardia Atrial fibrillation or flutter High output heart failure
Gastrointestinal	Diarrhea Yellowish sclera	Hyperactive bowel sound Jaundice
Reproductive	Oligomenorrhea Decreased libido	Gynecomastia Telangiectasia
Gynecologic	Menorrhagia Irregularity	Sparse pubic hair
Hematologic	Pale skin	Anemia Leukocytosis
Dermatologic	Hair loss	Pretibial myxedema† Warm, moist skin Palmar erythema Onycholysis

†Pretibial myxedema may present in 5% of patients with Graves' disease.

heard. Direct inotropic and chronotropic effects of thyroid hormone on the heart cause increased blood volume, contractility, and cardiac output. Enhanced contractility produces elevations in systolic blood pressure and pulse pressure, leading to a dicrotic or water-hammer pulse. Atrial fibrillation occurrence ranges between 10% and 35% of thyrotoxicosis cases.[6,7]

Exophthalmos is present in Graves' disease. The severity of ophthalmopathy does not necessarily parallel the magnitude of thyroid dysfunction but reflects the responsible autoimmune process. Not all hyperthyroidism patients present with goiter. A goiter is not present with exogenous administration of thyroid hormone and apathetic thyrotoxicosis (without obvious clinical manifestations). Likewise, the presence of a goiter does not necessarily confirm the diagnosis of thyrotoxicosis. Thyroid gland tenderness can be found in inflammatory conditions such as subacute thyroiditis (de Quervain's thyroiditis).[8]

Diagnosing thyroid storm

Thyroid storm is a clinical diagnosis for patients with preexisting hyperthyroidism. In determining whether or not a patient has thyroid storm the main systems to concentrate on are the CNS (ranging from being agitated to seizure), thermoregulatory system (rise in temperature), cardiovascular system (ranging from tachycardia to atrial fibrillation and congestive cardiac failure [CCF]), and gastrointestinal–

Table 2. Burch and Wartofsky's diagnostic parameters and scoring points for thyroid storm

Diagnostic parameters	Scoring points
1. Thermoregulatory dysfunction	
Temperature, °C (°F)	
37.2–37.7 (99–99.9)	5
37.7–38.3 (100–100.9)	10
38.3–38.8 (101–101.9)	15
38.9–39.4 (102–102.9)	20
39.4–39.9 (103–103.9)	25
≥40 (≥104.0)	30
2. Central nervous system effects	
Absent	0
Mild (agitation)	10
Moderate (delirium, psychosis, extreme lethargy)	20
Severe (seizures, coma)	30
3. Gastrointestinal–hepatic dysfunction	
Absent	0
Moderate (diarrhea, nausea/vomiting, abdominal pain)	10
Severe (unexplained jaundice)	20
4. Cardiovascular dysfunction	
Tachycardia, b.p.m.	
90–109	5
110–119	10
120–139	15
≥140	25
5. Congestive heart failure	
Absent	0
Mild (pedal edema)	5
Moderate (bibasilar rales)	10
Severe (pulmonary edema)	15
6. Atrial fibrillation	
Absent	0
Present	10

Scoring system: ≥45, highly suggestive of thyroid storm; 25–44, suggestive of impending storm; <25, unlikely to represent thyroid storm. Table reproduced from: Burch & Wartofsky (1993).[5]

hepatic system (ranging from nausea to vomiting and jaundice). In an effort to standardize and objectify thyroid storm as compared with severe thyrotoxicosis, Burch and Wartofsky delineated a point system assessing degrees of dysfunction in these four major systems (Table 2).[5] The point system assists in determining whether the patient's presentation is unlikely, suggestive, or highly suggestive of thyroid storm. According to the system, any scores of 45 or more are highly suggestive of thyroid storm. The system is sensitive in picking up thyroid storm but not very specific.

In 2012, Akamizu *et al*.[1] formulated diagnostic criteria for thyroid storm and clarified its clinical features, prognosis, and incidence based on nationwide surveys in Japan. The diagnostic criteria determines whether a patient is a suspect or definite case of thyroid storm. *"Definite" thyroid storm* is defined as having laboratory evidence of increased free thyroid hormones with any CNS symptoms like restlessness, delirium, mental aberration, psychosis, somnolence, lethargy, convulsion, coma, scores ≥1 on Japan Coma Scale or scores ≤14 on Glasgow Coma Scale (listed in 2a of Table 3) and at least *one* non-CNS symptom listed below:

1. fever (≥38°C),
2. tachycardia (≥130 b.p.m.)
3. CCF presentation
4. gastrointestinal–hepatic derangement manifestations.

Alternatively, with no CNS symptoms, *"definite"* thyroid storm is also defined with at least *three* of the above manifestations and laboratory evidence of increased thyroid hormones. *"Suspect" cases of thyroid storm* are defined as those that fulfill the definite criteria but with undetermined status of raised thyroid hormones, while having history of thyroid disease with exophthalmos and goiter. This diagnostic criteria is simplified in Table 3. Nevertheless, these diagnostic criteria are not entirely applicable if other underlying diseases are clearly causing any of the following symptoms:

1. fever
2. impaired consciousness
3. existing heart failure
4. liver disorders

As some of these disorders may themselves be triggers for thyroid storm, symptoms that are difficult to determine as being caused by underlying disease should be regarded as being due to thyrotoxic crisis. Diagnose elderly patients carefully as they may have *apathetic thyroid storm* (not manifesting typical high fever and hyperactivity).

Differential diagnosis

The differential diagnosis of thyroid storm includes infection, sepsis, cocaine use, psychosis, pheochromocytoma, neuroleptic malignant syndrome, and hyperthermia.

Laboratory evaluation

Serum TSH level

In primary hyperthyroidism, the TSH level is low as a result of the negative feedback mechanism towards a high thyroid hormone level. Nevertheless, a low TSH level by itself is not diagnostic, as serum TSH may be reduced as a result of chronic liver or renal disease, or the effect of certain drugs like glucocorticoids, which reduce TSH secretion. The TSH level may be low or normal in exogenous causes of thyrotoxicosis.

Table 3. Akamizu's diagnostic criteria and features of thyroid storm†

No.	Diagnostic elements for thyroid storm	
Pre-requisite for diagnosis of thyroid storm		
1	Elevated serum free T3 or free T4	
Signs and symptoms		
2a	CNS manifestations	
		Any one of below: • Restlessness • Delirium • Mental aberration • Psychosis • Somnolence • Lethargy • Convulsion • Coma • Scores 1 or higher on the Japan Coma Scale • Scores 14 or lower on the Glasgow Coma Scale
2b	Non-CNS manifestations	
	Fever	**≥38°C**
	Tachycardia	**≥130 b.p.m.** (includes tachyarrhythmias such as atrial fibrillation)
	CCF	**Any one of below**: • Pulmonary edema • Moist rales for more than half the lung field • Cardiogenic shock • Class IV by the New York Heart Association • Class III or higher by the Killip classification
	Gastrointestinal and hepatic	**Any one of below**: • Nausea • Vomiting • Diarrhea • Jaundice • Serum bilirubin >3 mg/dL
Diagnosis		
3	**Definite**	Elevated thyroid hormones + any **CNS (1)** symptoms in **(2a)** + **one** or more of any of non-CNS manifestations in **(2b) OR** Elevated thyroid hormones **(1)** + **three** or more of any of non-CNS manifestations in **(2b)**
4	**Suspect**	Fulfilling "definite criteria" as above **BUT** raised thyroid hormone could not be determined + history of thyroid disease + exophthalmos + goiter

†Table reproduced by the author with modification and reference based on Akamizu *et al*. (2012).[1] CCF, congestive cardiac failure; CNS, central nervous system; T3, triiodothyronine; T4, thyroxine.

In secondary hyperthyroidism, TSH is increased because of increased production in the pituitary.

Free thyroid hormone levels: free T4 and T3

A low TSH with an elevated free thyroxine (FT4) level confirms primary hyperthyroidism. However, be cautioned that extrinsic causes may yield similar results. A high TSH with high FT4 denotes secondary causes of hyperthyroidism. A low TSH with a normal FT4 but elevated free triiodothyronine (FT3) is diagnostic of T3 thyrotoxicosis. T3 thyrotoxicosis occurs in <5% of patients who have thyrotoxicosis in North America.[9]

Total thyroid hormone level of thyroxine and triiodothyronine

Total serum T4 and T3 (bound and unbound) are increased in thyrotoxicosis. Eighty percent of circulating T3 is derived from monodeiodination of T4 in peripheral tissues, whereas 20% emanates from direct thyroidal secretion. Both T4 and T3 are then bound to proteins in the form of thyroid binding globulin, transthyretin, and albumin. Only a small fraction of the hormones are free and unbound. Laboratory measurement of total T3 and total T4 measures mainly protein-bound hormone concentrations. In thyroid storm, the total thyroid hormone level may or may not be increased. Results also may be affected by conditions that affect protein binding. However, with improved assays for FT4 and FT3, there is now little indication to measure total T3 and total T4.

Drug interactions in thyrotoxicosis patients

Many drugs interfere with protein binding, including heparin, furosemide, phenytoin, carbamazepine, diazepam, salicylates, opiates, estrogens, and NSAIDs. Because of this interference with total thyroid hormone levels, free hormone concentrations are preferable in the diagnosis of thyrotoxicosis.[9]

Laboratory confirmation test for Graves' disease

For laboratory confirmation of Graves' disease, the anti-TSH receptor antibody or thyroid-stimulating antibody test would be positive. Elevated radioactive iodine (or $99mTcO4^-$) uptake to the thyroid gland would be shown in Graves' disease.

Other investigations and comorbid abnormality considerations

Complete blood count, electrolytes, glucose, renal, and liver function tests should be considered to identify comorbid abnormalities, but treatment has to start upon suspicion of the diagnosis. In thyroid storm, complete blood count typically shows leukocytosis with shift to the left. Mild hypercalcemia and elevated alkaline phosphatase can occur because of hemoconcentration and enhanced thyroid hormone-stimulated bone resorption.[9]

Thyrotoxicosis also induces liver enzyme metabolism, causing raised liver enzymes.

A high serum cortisol value is an expected finding in thyrotoxic individuals. This should be the normal reaction of an adrenal gland to a body under stress. The finding of an abnormally low cortisol level in a patient with Graves' disease should raise suspicion of coincidental adrenal insufficiency.

Imaging

Chest radiograph can be done to rule out infectious source as precipitant for thyroid storm. A thyroid sonogram can be done to assess thyroid gland size, vascularity, and the presence of nodules. Typically, a thyroid gland secreting excessive hormones would be enlarged. However, in the setting of subacute, postpartum thyroiditis, silent thyroiditis, or exogenous causes of hyperthyroidism, the thyroid gland is not expected to be enlarged. Nuclear medicine imaging with iodine-131 would reveal a greatly increased uptake of radioiodine as early as 1 or 2 h after administration of the agent. Computed tomography scan of the brain may be necessary to exclude neurologic conditions as secondary causes of hyperthyroidism.

Electrocardiography in thyrotoxicosis

Electrocardiographic findings in thyrotoxicosis most commonly include sinus tachycardia and atrial fibrillation. Sinus tachycardia occurs in approximately 40% of cases.[7] Atrial fibrillation occurs in 10–35% of thyrotoxicosis patients, with a tendency to occur more commonly in patients >60 years old who are more likely to have underlying structural heart disease.[7] Premature ventricular contractions and heart blocks may be present. Atrial premature contractions and atrial flutter may also occur in thyrotoxicosis.

Treatment for thyroid storm

Treatment of thyroid storm has multiple aims:

1. supportive care
2. inhibition of new hormone synthesis
3. inhibition of thyroid hormone release
4. peripheral β-adrenergic receptor blockade
5. preventing peripheral conversion of T4 to T3
6. identifying and treating precipitating factors.

The treatment recommendations are shown in Table 4, with specific comments in the following sections.

Treatment aim 1: supportive care

Fluid losses could result from the combination of fever, diaphoresis, vomiting, and diarrhea. Normal saline can be given for replacement. Check blood glucose and if blood sugar is relatively low, i.v. fluids with dextrose (isotonic saline with 5% or 10% dextrose) may be given to replenish glycogen stores.

Treatment aim 2: inhibition of new thyroid hormone synthesis

Thionamides Thionamides used for the treatment of thyrotoxicosis are either methimazole or propylthiouracil (PTU). Thionamide therapy decreases the synthesis of new hormone production but also has immunosuppressive effects.[10]

Table 4. Treatment for thyroid storm

1. Supportive care

General: oxygen, cardiac monitoring

Fever: external cooling; acetaminophen, 325–650 mg PO/PR every 4–6 h (aspirin is contraindicated as it releases thyroxine from protein binding sites)

Dehydration: i.v. isotonic saline (use dextrose containing isotonic saline if blood sugar low)

Nutrition: glucose, multivitamins, thiamine, and folate can be considered (deficient secondary to hypermetabolism)

2. Inhibition of new thyroid hormone synthesis with thionamides

Methimazole, 40 mg given PO as loading dose followed by 25 mg every 4 h. Total daily dose: 120 mg/day. If given PR, 40 mg should be crushed in aqueous solution. Alternative: carbimazole 40–60 mg given PO initially, followed by maintenance between 5–20 mg daily (avoid methimazole and carbimazole for pregnant women in first trimester as they have a teratogenic effect. It can only be used in second and third trimesters of pregnancy)

or

PTU, a loading dose of 600–1,000 mg given PO followed by 200–250 mg every 4 h. Total daily dose: 1,200–1,500 mg/day. Drug can be given through nasogastric tube or PR. PTU also blocks peripheral conversion of T4 to T3 (avoid in patients with liver disease or in second or third trimester of pregnancy)

3. Inhibition of thyroid hormone release (at least 1 h after thionamides given)

Lugol solution, 8–10 drops PO every 6–8 h

or

Potassium iodide (SSKI), five drops PO every 6 h

or

I.v. iopanoic acid, 1 g every 8 h for first 24 h, then 500 mg twice a day

or

Ipodate, 0.5–3 g/day PO (especially useful with thyroiditis or thyroid hormone overdose).

or

Lithium carbonate (if allergic to iodine or agranulocytosis occurs with thionamides), 300 mg PO every 6 h (1,200 mg/day). Serum lithium should be monitored within safe range

4. β-adrenergic receptor blockade

Propranolol, i.v. in slow 1–2-mg boluses, may be repeated every 10–15 min until desired effect is achieved. For less toxic patient, PO dose of 20–120 mg per dose or 160–320 mg/day in divided doses

or

Esmolol, 500 μg/kg i.v. bolus, then 50–200 μg/kg/min maintenance.

or

Reserpine, 2.5–5.0 mg i.m. every 4–6 h, preceded by 1-mg test dose while monitoring blood pressure (consider if β-blocker contraindicated but avoid in congestive heart failure or hypotension)

or

Guanethidine, 30–40 mg PO every 6 h (consider if β-blocker contraindicated but avoid in congestive heart failure, hypotension, and cardiac shock)

5. Preventing peripheral conversion of T4 to T3

Hydrocortisone, 100 mg i.v. initially, then 100 mg three times/day until stable (also for adrenal replacement due to hypermetabolism)

or

Dexamethasone, 2 mg i.v. every 6 h

6. Treat precipitating event

All triggers of thyroid storm should be searched and treated accordingly (infection, myocardial infarct, diabetic ketoacidosis, etc.)

7. Definitive therapy

Radioactive iodine ablation therapy or surgery may be necessary in suitable patients

Replacement therapy: dialysis and plasmapheresis are last resorts for patients who do not respond to above treatments. PO, per oral; PR, per rectal; PTU, propylthiouracil; T3, triiodothyronine; T4, thyroxine.

Thionamides inhibit synthesis of thyroid hormones by preventing organification and trapping of iodide to iodine and by inhibiting coupling of iodotyrosines.

Methimazole has a longer half-life than PTU, permitting less frequent dosing. It presents in free form in the serum whereas 80–90% of PTU is bound to albumin.[10]

The dose for methimazole is 40–100 mg given orally as the loading dose followed by 20 mg every 4 h. The total daily dose is 120 mg. If given rectally, 40 mg should be crushed in aqueous solution. Although there are no commercially available parenteral formulations of the thionamides, there are case reports of methimazole being administered i.v. in circumstances in which the oral or rectal routes could not be used.[11] Methimazole was shown to have similar pharmacokinetics for both oral and i.v. use in normal subjects and in subjects with hyperthyroidism. In some centers, only carbimazole is available, which is the pro-drug of methimazole. If methimazole is not available, carbimazole can be used with the same potency.[12] The initial dose is 40–60 mg, followed by a maintenance dose of between 5 and 20 mg daily.

As for PTU, the dose for thyroid storm is 600–1,000 mg given orally as a loading dose followed by 200–250 mg every 4 h. The total daily dose is between 1,200 and 1,500 mg. The drug can be given through a nasogastric tube or rectally. Outside the thyroid gland, only PTU, not methimazole, can inhibit conversion of T4 to T3.

Adverse Side Effects from Antithyroid Drugs

Since 2010, the US Food and Drug Administration has added a boxed warning to the prescribing information of PTU to include information about reports of severe liver injury and acute liver failure, some of which have been fatal, in adult and pediatric patients using this medication.[13] The US Food and Drug Administration recommends that PTU be reserved for patients who cannot tolerate methimazole. PTU is preferred only in the case of pregnant women during the first trimester as methimazole use during this period had been associated with teratogenicity.[14] Nevertheless, methimazole is suggested for use during the second and third trimesters of pregnancy.

Treatment aim 3: inhibition of hormone release

Iodine Lugol solution, potassium iodide, or ipodate can be given to stop thyroid hormone release. Thionamide therapy must be instituted first, and these drugs only given at least 1 h later. Iodine therapy blocks the release of prestored hormone and decreases iodide transport and oxidation in follicular cells. Lugol solution can be given three to four times to a total of 30–40 drops/day. Initial treatment may start with 8–10 drops. Lugol solution provides 8 mg iodide/drop.

Iodinated radiographic contrast dyes that contain ipodate 0.5–3 g/day orally, or i.v. iopanoic acid 1 g every 8 h for the first 24 h followed by 500 mg twice a day, have been used to inhibit hormone release; they also have the added property of effectively preventing conversion of T4 to T3. Nevertheless, iodine-containing solution should not be given to patients with iodine overload or iodine-induced hyperthyroidism, or those with amiodarone-induced thyrotoxicosis. An alternative such as lithium or potassium perchlorate may be used instead.

Lithium In situations in which there is a contraindication to giving iodine (for example, hypersensitivity to iodine), an alternative like lithium can be used. In severe thyroid storm conditions, lithium can also be used in combination with PTU or methimazole. Lithium inhibits thyroid hormone release from the thyroid gland as well as decreasing thyroid hormone synthesis. In thyroid storm, the dosing for lithium is 300 mg every 8 h. Lithium levels should be monitored to avoid toxicity.

Treatment aim 4: preventing peripheral conversion of thyroxine to triiodothyronine

The peripheral conversion of T4 to T3, which is responsible for 80% of T3 present in the circulation, is blocked by PTU, propranolol, and glucocorticoid. Nevertheless, for PTU and propranolol, this effect is not quantitatively significant. Therefore, glucocorticoids like hydrocortisone or dexamethasone are essential in treatment. Glucocorticoid use in thyroid storm also improves survival rates.[3,5] In patients who have severe thyrotoxicosis, especially in conjunction with hypotension, treatment with glucocorticoids is a standard practice because of the possibility of relative adrenal insufficiency.

Treatment aim 5: β-adrenergic receptor blockade

Propranolol can be given i.v. in slow 1–2 mg boluses, which may be repeated every 10–15 min until the desired effect is achieved. Orally, propranolol therapy usually begins at 20–120 mg per dose, or 160–320 mg/day in divided doses.

The contraindications to peripheral blockade are the same as for other medical conditions. Exercise caution in patients with CCF and thyrotoxic cardiomyopathy. Complicated patients with both a tachydysrhythmia and congestive heart failure can be managed first with rate control and an inotropic agent.

Treatment aim 6: identifying precipitating factors

A vigorous search for an infectious source would be warranted in febrile thyrotoxic patients. This could be done with blood, urine, throat, and sputum cultures. A chest radiograph should be done to rule out chest infection. An electrocardiogram may be done to rule out myocardial infarction, ischemia, or arrhythmia.

In cases of thyroid storm precipitated by diabetic ketoacidosis, myocardial infarction, pulmonary embolism, or other acute processes, appropriate management of the specific underlying problem should proceed along with the treatment of the thyrotoxicosis.[5]

Consequent management and definitive therapy

As the thyrotoxic patient shows clinical improvement with therapy, some of the treatment methods can be modulated or withdrawn. Iodine therapy can be discontinued, and glucocorticoids can be tapered. Thionamide therapy, at gradually decreasing doses, is usually required for weeks to months after thyroid storm to attain euthyroidism. β-Adrenergic blockade is also needed while the patient is still thyrotoxic.

Definitive therapy with radioactive iodine ablation may not be administered for several weeks or months following treatment with iodine for thyroid storm. After the resolution of thyroid storm, the thyrotoxic patient continues to require close follow-up and monitoring, with plans for definitive therapy to prevent a future recurrence of life-threatening thyrotoxicosis.[5]

GUIDE FOR PREPARATION OF THYROTOXIC PATIENTS FOR EMERGENCY SURGERY

IN THE EVENT that a patient has a background of thyrotoxicosis and requires emergent surgery, the recommendation of drug supplementation is as shown in Table 5. The supplementation is important, as surgery in a patient with hyperthyroidism may precipitate thyroid storm.

Disposition and follow-up

All thyroid storm patients ideally require admission to the intensive care unit or at least a high dependency unit. Patients with thyroid storm often have concomitant diseases precipitating the attack and requiring close monitoring.

Table 5. Rapid preparation of thyrotoxic patients for emergent surgery

Drug class	Recommended drug	Dosage	Mechanism of action	Continue postoperatively?
β-Adrenergic blockade	Propranolol	40–80 mg PO 3–4 times/day	β-Adrenergic blockade; decreased T4 to T3 conversion (high dose)	Yes
	or			
	Esmolol	50–100 μg/kg/min	β-Adrenergic blockade	Change to PO propranolol
Thionamide	Propylthiouracil	200 mg PO every 4 h	Inhibition of new thyroid hormone synthesis; decreased T4 to T3 conversion	Stop immediately after near-total thyroidectomy; continue after non-thyroidal surgery
	or			
	Methimazole	20 mg PO every 4 h	Inhibition of new thyroid hormone synthesis	Stop immediately after near-total thyroidectomy; continue after non-thyroidal surgery
Oral cholecystographic agent	Iopanoic acid	500 mg PO twice a day	Decreased release of thyroid hormone; decreased T4 to T3 conversion	Stop immediately after surgery
Corticosteroid	Hydrocortisone	100 mg PO or i.v. every 8 h	Vasomotor stability; decreased T4 to T3 conversion	Taper over first 72 h
	or			
	Dexamethasone	2 mg PO or i.v. every 6 h	Vasomotor stability; decreased T4 to T3 conversion	Taper over first 72 h
	or			
	Betamethasone	0.5 mg PO every 6 h, i.m. or i.v.	Vasomotor stability; decreased T4 to T3 conversion	Taper over first 72 h

Table sourced from Langley & Burch (2003).[15] PO, per orally; T3, triiodothyronine; T4, thyroxine.

Complete recovery may take 1 week until circulating levels of thyroid hormones are depleted. Stable hyperthyroid patients with minimal symptoms can only be discharged for follow-up either by an endocrinologist or primary care physician, if the patient is already on medication with a clear plan of follow-up.

MANAGEMENT OF SPECIAL GROUPS OF PATIENTS WITH THYROTOXICOSIS

Atrial fibrillation in thyroid storm

β-Blockers such as propranolol used in thyroid storm could limit the rate as well as reducing the peripheral conversion of T4 to T3. Alternatively, esmolol, with a shorter acting effect could also be used. Intravenous calcium channel blockers may be considered if β-blockers are contraindicated but should be used cautiously, as these may cause severe hypotension and a further reduction in systemic vascular resistance that is already low in patients with thyrotoxicosis. Digoxin can also be used to slow the ventricular response rate in atrial fibrillation. However, higher doses may need to be considered as there is increased renal clearance and increased Na/K ATPase units in myocardium.[13,16] Alternatively, amiodarone is effective for chemical cardioversion of atrial fibrillation, even when the dysrhythmia is refractory to other drugs.[14,17] In combination with PTU, amiodarone accelerates reduction of serum concentration of T3 and its conversion from T4, which would be an added benefit.[18] Nevertheless, amiodarone treatment has also been cited in published reports as a precipitant of thyroid storm. It is 37% organic iodine by weight and, as such, can have many effects on thyroid function. Normal maintenance doses result in iodine loads of 10–20 times the normal dietary requirement of iodine. Chronic use of amiodarone causes either a hypothyroid or a thyrotoxic state in 20–30% of patients.[19] Therefore, in view of its iodine-rich benzfuran content, amiodarone should not be the first line of treatment as there are potential confounding effects of iodine on thyrotoxicosis. If amiodarone is to be used, thionamides should be given first and it is safer to delay its use to at least 1 h after thionamides have been prescribed.

Thromboembolism in thyrotoxicosis patient with atrial fibrillation

In a large retrospective study of thyrotoxicosis with atrial fibrillation, it appears these patients are not at greater risk for embolic events compared with age-matched patients who have atrial fibrillation due to other causes.[20] However, the incidence of thromboembolism in thyrotoxic patients is considerable. In view of the procoaguable state and increased incidence of mitral valve prolapse in thyrotoxicosis-related atrial fibrillation, anticoagulant should be started.[21,22] Heparinization should be instituted in the first instance, followed by warfarin. Lower dose warfarin is needed as there is reduced level of vitamin K- dependent clotting factors in thyrotoxicosis.[23,24]

Congestive cardiac failure (CCF)

Heart failure in thyrotoxicosis is well recognized. Thyrotoxicosis is associated with a high cardiac output state and heart failure in this context is usually associated with underlying cardiac disease. Initial management of CCF with thyrotoxicosis is with loop diuretics. Vasodilators such as nitrates should be avoided as thyrotoxicosis is associated with vasodilatation and systemic vascular resistance.[25] Avoid β-adrenoceptor blockers when the cardiac failure is truly congestive with underlying ischemic, hypertensive, or valvular heart disease. In this situation, esmolol use would be safer as it has a short half-life. The drug could be withdrawn and the effect restored quickly if there is hypotension.[26,27]

CONFLICT OF INTEREST

NONE.

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