

# CASE REPORT

## Heparin Management in a Patient with Thyroid Storm

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Management of atrial fibrillation during thyroid storm includes anticoagulation for risk of clot propagation. Physiologic changes that occur in patients with thyroid storm may lead to heparin resistance and inappropriate anticoagulation. Factors contributing to heparin resistance include antithrombin deficiency, increased heparin clearance, and increased levels of factor VIII. We describe a 30-year-old woman who was hospitalized with thyroid storm. She subsequently developed atrial fibrillation, and unfractionated heparin was started. Over the next 4 days, the heparin infusion rate was titrated to an exaggerated dose of 2100 units/hour (33 units/kg/hr) in order to attain a therapeutic response. By hospital day 7, her atrial fibrillation had resolved; the heparin infusion was discontinued, and the patient remained clinically stable with no sequelae. The exact mechanism of heparin resistance in thyroid storm is unknown; however, data have shown a positive correlation between factor VIII and thyroxine levels. This patient had an elevated thyroxine level of 32.5 µg/dl, which suggested that an increased factor VIII level was the probable mechanism of heparin resistance. Recognition of possible heparin resistance in patients with thyroid storm will allow clinicians to promptly identify appropriate interventions to ensure adequate anticoagulation in this high-risk patient population.

**Key Words:** hyperthyroidism, thyroid storm, unfractionated heparin, UFH, heparin resistance, activated partial thromboplastin time.

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Since its inception in the early 1900s, unfractionated heparin (UFH) has been the cornerstone of treatment for multiple modalities including venous thromboembolism and atrial fibrillation. Unfractionated heparin is a sulfated polysaccharide with a molecular weight ranging from 3000–30,000 daltons and a mean weight of 15,000 daltons (~45 saccharide units).<sup>1, 2</sup> The agent accomplishes its anticoagulant effects by covalently and irreversibly binding to antithrombin by means of lysine residues, producing a conformational change at the

arginine-reactive center, making antithrombin a more potent inhibitor.<sup>1–3</sup> Unfractionated heparin also binds to positively charged surfaces such as plasma proteins, macrophages, and endothelial cells, thus making the pharmacologic and pharmacokinetic characteristics and monitoring parameters of UFH variable.<sup>1, 3–5</sup>

The variability in the pharmacokinetics of UFH may be confounded by comorbidities such as thyroid disorders. The interactive properties of warfarin sodium and the hyperthyroidic state have been documented, with a proposed mechanism of increased catabolism of vitamin K–dependent clotting factors.<sup>6, 7</sup> Conversely, the interaction of UFH and hyperthyroidism has not been fully elucidated in the contemporary literature.<sup>8</sup>

Treatment of thyroid storm consists of symptomatic treatment with nonselective β-blockers, thionamides, and, when atrial fibrillation is evident, anticoagulation. The

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occurrence of atrial fibrillation in patients with hyperthyroidism has been reported to range from 5–15%, with an increase in occurrence as age enters the 6th decade.<sup>9</sup> Anticoagulation in these patients is controversial, and the risk of bleeding during anticoagulation therapy must be weighed against the risk of systemic embolization.<sup>9</sup>

We describe a patient with thyroid storm complicated by atrial fibrillation who exhibited a notable effect on UFH dosing, suggesting a resistant etiology.

### Case Report

A 30-year-old Hispanic woman (weight 64 kg) came to the emergency department with complaints of dysphagia, cough, streaky bloody sputum, and palpitations for the past several weeks. On examination, she was noted to have an enlarged thyroid gland and was in mild distress. Her medical history was significant for hyperthyroidism and bipolar disorder type I. Her drug therapy consisted of trazodone 150 mg at bedtime, escitalopram 40 mg/day, quetiapine 50 mg twice/day, propylthiouracil 100 mg 3 times/day, and propranolol 40 mg 3 times/day. The patient denied tobacco use.

On admission, the patient's vital signs were a body temperature of 99.4°F, blood pressure 150/108 mm Hg, respiratory rate 25 breaths/minute, heart rate 200 beats/minute in an irregularly irregular pattern, and an oxygen saturation of 99% on room air. Electrocardiography revealed atrial fibrillation. Laboratory values were serum sodium 141 mEq/L (normal range 135–145 mEq/L), potassium 3.3 mEq/L (3.5–5 mEq/L), chloride 109 mEq/L (96–106 mEq/L), bicarbonate 24 mEq/L (22–30 mEq/L), BUN 6 mg/dl (8–18 mg/dl), creatinine 0.2 mg/dl (0.5–1.2 mg/dl), and glucose 113 mg/dl (70–110 mg/dl); white blood cell count  $7.5 \times 10^3/\text{mm}^3$  ( $4.0\text{--}10.0 \times 10^3/\text{mm}^3$ ) with a normal differential, hemoglobin 9.9 g/dl (12–16 g/dl), hematocrit 30.8% (37–47%), platelet count  $186 \times 10^3/\text{mm}^3$  ( $150\text{--}350 \times 10^3/\text{mm}^3$ ); and activated partial thromboplastin time (aPTT) 19.9 seconds (22–35 sec).

Thyroid function test results were a thyroid-stimulating hormone less than 0.04  $\mu\text{IU}/\text{ml}$  (normal range 0.3–4.2  $\mu\text{IU}/\text{ml}$ ), thyroxine ( $T_4$ ) 32.5  $\mu\text{g}/\text{dl}$  (5–10  $\mu\text{g}/\text{dl}$ ), total triiodothyronine ( $T_3$ ) 609 ng/dl (79–149 ng/dl), thyroxine-binding globulin 14.7  $\mu\text{g}/\text{dl}$  (19–28  $\mu\text{g}/\text{dl}$ ), and estimated free thyroxine 10.3 ng/dl (1.0–2.2 ng/dl). Based on the patient's signs and symptoms in the

emergency department as well as a thyroid storm criteria score of 55 ( $\geq 45$  is highly suggestive of thyroid storm),<sup>10</sup> the diagnosis of thyroid storm was made, and medical management was initiated.

Treatment was started with a loading dose of propylthiouracil 600 mg followed by 300 mg every 6 hours. In addition, the patient received Lugol's solution 10 drops 3 times/day, intravenous hydrocortisone 100 mg every 8 hours, and a cumulative dose of intravenous propranolol 6 mg administered over several hours. Based on the institution's suggested guidelines for treatment of atrial fibrillation, anticoagulation with UFH was initiated, with a loading dose of 5000 units followed by an initial maintenance infusion rate of 1000 units/hour.

Several hours after presentation to the emergency department, the patient became increasingly agitated and tachypnic; a chest radiograph showed pulmonary vascular engorgement, effusions, and a questionable pneumonia. The decision was made to intubate the patient for airway protection and transfer her to the medical intensive care unit (MICU).

In the MICU, intravenous ceftriaxone 1 g/day and doxycycline 100 mg twice/day were started empirically; her hyperthyroid regimen and UFH were continued. Due to continued tachycardia, propranolol was discontinued. Esmolol was initiated and titrated, with minimal response. A diltiazem infusion was subsequently added to the esmolol, leading to an adequate response.

Six hours after starting UFH, the patient's aPTT was 27.6 seconds (target level 55–90 sec); a bolus of UFH 5000 units was given. The UFH infusion was increased to 1200 units/hour based on the institutional UFH protocol. Seven hours after this dosage adjustment, the aPTT was again subtherapeutic (28.7 sec), and another UFH bolus of 5000 units was given. The UFH infusion was increased to 1400 units/hour. Over the next 2 days, the UFH dosage was adjusted until an appropriate therapeutic response was achieved with a final dose of 2100 units/hour (33 units/kg/hr) (Table 1). The patient returned to normal sinus rhythm on hospital day 7. Echocardiographic studies showed no evidence of clot burden. Her  $T_4$ ,  $T_3$ , and estimated free thyroxine levels at that time remained elevated (11.3  $\mu\text{g}/\text{dl}$ , 234 ng/dl, and 2.9 ng/dl, respectively), although the patient was clinically stable. The UFH was discontinued, and the patient underwent a thyroidectomy, with no sequelae

Table 1. Heparin Dosing and Monitoring Parameters Throughout the Patient's Hospitalization

Hospital Day	Time	aPTT (sec) <sup>a</sup>	UFH Bolus (units)	UFH Infusion Rate (units/hr)	INR <sup>b</sup>
1	12 P.M.	19.9	5000	1000	1.30
	6 P.M.	27.6	5000	1200	1.40
2	1 A.M.	28.7	5000	1400	
	9 A.M.	29.8	5000	1600	
	4 P.M.	39.9	1800	1700	1.39
3	2 A.M.	49.7	—	1800	1.41
	11 A.M.	50.1	—	1900	1.60
	4 P.M.	49.9	—	2100	1.74
4	5 P.M.	70.0	—	2100	1.87
5	4 A.M.	78.2	—	2100	1.64
6	8 A.M.	79.8	—	2100	1.66
7	5 A.M.	83.0	—	2100	1.62

aPTT = activated partial thromboplastin time; UFH = unfractionated heparin; INR = international normalized ratio.

<sup>a</sup>aPTT target level was 55–90 sec.

<sup>b</sup>INR target range was 0.9–1.4.

related to the thyroid storm.

## Discussion

Heparin resistance is defined as either an inability to achieve an activated clotting time (ACT) above 480 seconds after a cumulative UFH dose of 450 units/kg<sup>4, 11</sup> or the need for more than 35,000 units of UFH/24 hours<sup>1, 5, 12</sup> to achieve a therapeutic aPTT. Activated clotting time values differ from aPTT values with respect to their precision at different heparin concentrations. For example, during coronary artery bypass graft surgery, UFH is administered at high doses, making aPTT values inaccurate when heparin concentrations exceed 1.0 units/ml. The ACT overcomes this limitation by the addition of an activating agent (e.g., kaolin), and the anticoagulation response of UFH can be measured at higher concentrations.

Several mechanisms for heparin resistance have been postulated and include a decrease in antithrombin level, increased UFH clearance, and elevations in factor VIII concentrations.<sup>1, 4, 12, 13</sup>

Anticoagulant effects of heparin are insufficient as the plasma antithrombin concentration falls below 60%.<sup>4</sup> With a lack of binding ligand (antithrombin), heparin cannot exert its pharmacologic response, rendering the drug ineffective.<sup>1, 3</sup> Conditions that may predispose patients to antithrombin deficiency include chronic liver disease, an acute inflammatory process, nephrotic syndrome, and disseminated intravascular coagulation.<sup>14</sup> Moreover, predictors of acquired heparin resistance include antithrombin level below 60%, use of preoperative subcutaneous heparin, use of intravenous

heparin, platelet count of at least 300 x 10<sup>3</sup>/mm<sup>3</sup>, age 65 years or older, low albumin level, and low baseline ACT.<sup>10, 11, 14</sup> If all predictors are present, the likelihood of heparin resistance is shown to be 99%. With the absence of all these predictors, the likelihood of heparin resistance is 10%.

Increased UFH clearance has been reported in patients with venous thrombosis and pulmonary embolism.<sup>13</sup> Mechanisms explaining this phenomenon have not been postulated; however, investigators suggest differences in the degree of platelet adhesion to thrombi.<sup>13</sup> As more thrombin is formed on the surface of emboli, clearance rates of heparin may be increased by a release of antiheparin activity from platelets exposed to thrombin.<sup>13</sup>

Factor VIII is essential for the intrinsic pathway of coagulation, with inappropriate elevations accelerating the cleavage of factor X by factor IXa, leading to a presumed increase in clot formation. Factor VIII is considered an acute-phase reactant that elevates during times of stress, pregnancy, and liver disease. Of note, elevations in factor VIII concentrations have been associated with low aPTT values.<sup>15, 16</sup>

The mechanism for heparin resistance in patients with hyperthyroidism has not been fully elucidated; although, theories regarding the relationship between coagulation factors and morbidities of the thyroid gland have been studied.<sup>15–19</sup> Hyperthyroidism has been documented to increase prothrombin time and international normalized ratio (INR) values due to its enhanced metabolism of clotting factors, with a normalization of these factors seen after treatment with antithyroid drugs.<sup>7, 16</sup> Literature

also supports the hypothesis of hyperthyroidism increasing the turnover of factors II, VII, and X, ultimately enhancing the effects of anticoagulants.<sup>17</sup> One group of investigators evaluated the relationship between coagulation and fibrinolysis during the hyperthyroidic state and noted increased levels of fibrinogen, factor VIII, factor IX, von Willebrand factor, antithrombin III, and plasminogen activating inhibitor-1, whereas concentrations of factor X and tissue plasminogen activator decreased.<sup>15, 18</sup> This relationship suggests a reduced fibrinolytic capacity in this patient population, leading to a hypercoagulable state.<sup>15, 17, 19</sup> Moreover, these data illustrate a positive correlation between the concentrations of factor VIII and T<sub>4</sub>.<sup>18</sup>

With regard to our patient's case of heparin resistance, our patient had no antithrombin deficiency predictors of heparin resistance such as a high platelet count, previous heparin use, or age 65 years or older. In addition, she did not have a history of liver or renal disease and showed no signs of disseminated intravascular coagulation. The aforementioned data support an increase in antithrombin concentrations in patients with hyperthyroidism, making the mechanism of depressed concentrations of antithrombin during thyroid storm unlikely. Increased heparin clearance may also be considered due to the high doses of UFH administered in our patient. At supratherapeutic concentrations, heparin chains with or without the specific pentasaccharide sequence containing a 3-O-sulfated glucosamine can catalyze thrombin inhibition by means of a second cofactor termed heparin cofactor II.<sup>1-3</sup> At even higher levels, heparin further inhibits factor Xa proliferation through antithrombin and heparin cofactor II independent pathways, namely inhibition of factor IXa, leading to increased INR values.<sup>1</sup> This mechanism is important only when the dosage of heparin exceeds recommended guidelines.<sup>1</sup> Because our patient's INR increased only as heparin dosages were titrated to 33 units/kg/hour (2100 units/hr), this may suggest that heparin resistance in this patient was not caused by increased clearance of heparin. Conversely, there may have been an accumulation of the UFH causing an inhibition of factor Xa through independent pathways.

Our patient had an initial estimated free thyroxine level of over 4-fold the normal value. With the interplay of factor VIII and T<sub>4</sub> concentrations, the hypothesis of high levels of factor VIII contributing to the disparity of aPTT

concentrations seems a more relevant etiology. In addition, our patient exhibited a shorter aPTT at baseline, which has been seen in patients with elevated factor VIII levels.<sup>1</sup> Given the current information, one may deduce that heparin resistance in this patient was caused by high levels of factor VIII, not a deficiency in antithrombin or increased UFH clearance.

Although an etiology for the events that transpired can be hypothesized, there are several limitations of this case report. As stated earlier, heparin cannot exert its physiologic response without complexing with antithrombin; therefore, antithrombin levels might have been useful to evaluate their role in the resistance pattern. Also, factor VIII concentrations were not measured, which might have strengthened the notion of this cofactor causing hyperthyroidic heparin resistance. With such high doses of UFH, monitoring the response with ACT levels might have been a more accurate way to assess UFH clearance.

## Conclusion

Limited data are available in the treatment of atrial fibrillation induced by thyroid storm, possibly due to the rarity of thyroid storm. In this case report, we describe an important consideration in the paradigm of thought related to UFH dosing and the hyperthyroidic state. Clotting factors that are associated with heparin resistance include factor VIII and antithrombin, which are altered during hyperthyroidism. Elevations in factor VIII levels may be the main culprit in the pharmacokinetic and pharmacodynamic changes observed during heparin administration in the hyperthyroidic state. Given the elevated dosage requirements of UFH needed to achieve a therapeutic aPTT and the erratic nature of clotting factor catabolism during thyroid storm, close monitoring of aPTT is warranted. It is important that clinicians understand the disease-drug interaction that can occur between thyroid storm and UFH, leading to thromboembolic events. Further data are needed to determine the most accurate method of managing anticoagulation in this population.

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