management of thyroid storm [created by Paul Young 02/12/07]

general

- The medical management of thyroid storm consists of an array of medications that act to halt the synthesis, release, and peripheral effects of thyroid hormone.
- Therapy has multiple targets: stopping synthesis of new hormone within the thyroid gland; halting the release of stored thyroid hormone from the thyroid gland; preventing conversion of T4 to T3; controlling the adrenergic symptoms associated with thyrotoxicosis; and controlling systemic decompensation with supportive therapy
- The order of therapy in treating thyroid storm is very important, with regard to use of thionamide therapy and iodine therapy. In most patients, inhibition of thyroid gland synthesis of new thyroid hormone with a thionamide should be initiated before iodine therapy, to prevent the stimulation of new thyroid hormone synthesis that can occur if iodine is given initially.

thionamides

- The two specific antithyroid agent classes are thiouracils and imidazoles. Propylthiouracil is a thiouracil, whereas methimazole and carbimazole are imidazoles. [Carbimazole is metabolized rapidly to methimazole]
- Within the thyroid gland, the thionamides interfere with the thyroperoxidase-catalyzed coupling process by which iodotyrosine residues are combined to form T4 and T3. Thionamides may also have an inhibitory effect on thyroid follicular cell function and growth.
- Outside the thyroid gland, propylthiouracil, but not methimazole, inhibits conversion of T4 to T3. Thionamides may also have clinically important immunosuppressive effects, including decreasing antithyrotropin-receptor antibodies over time, and decreasing other immunologically important molecules, such as intracellular adhesion molecule 1 and soluble interleukin-2.

- Methimazole has a longer half-life than propylthiouracil, permitting less frequent dosing. Either agent may be used to treat thyroid storm. Propylthiouracil has the additional theoretical advantage of inhibiting peripheral conversion of T4 to T3.
- The recommended dosing in thyroid storm for propylthiouracil is 800 to 1200 mg daily in divided doses of 200 mg or 300 mg every 6 hours (although smaller more frequent doses can be given). The dosing for methimazole is 80 to 100 mg daily in divided doses of 20 to 25 mg every 6 hours (although once stable, the frequency of dosing can be decreased to once or twice daily)

- Common adverse side effects of the antithyroid drugs include an abnormal sense of taste, pruritus, urticaria, fever, and arthralgias. More rare and serious side effects are agranulocytosis, hepatotoxicity, and vasculitis.
- With a criterion of absolute granulocyte count of less than 500 per cubic millimeter, 0.37% of subjects receiving propylthiouracil and 0.35% of subjects receiving methimazole developed agranulocytosis, in a large case series. Most cases of agranulocytosis occur within the first 3 months of treatment, but can occur anytime after starting therapy.
- Hepatotoxicity can also occur in 0.1% to 0.2% of patients using antithyroid drugs. Hepatotoxicity related to propylthiouracil tends to be an allergic hepatitis with evidence of hepatocellular injury, whereas hepatotoxicity related to methimazole tends to result in hepatic abnormalities typical of a cholestatic process. Vasculitis may also occur with antithyroid drug use, associated more commonly with propylthiouracil than with methimazole.

iodine

Mechanism of action
- In the setting of thyroid storm, iodine therapy complements the effects of thionamide therapy. Thionamide therapy decreases the synthesis of new hormone production; iodine therapy blocks the release of prestored hormone, and decreases iodide transport and oxidation in follicular cells.
- Small increments in available iodide cause increased formation of thyroid hormone; however, large amounts of exogenous iodide actually inhibit hormone formation. This decrease in organification due to increasing doses of inorganic iodide is known as the "Wolff-Chaikoff" effect. However, despite maintenance of high doses of iodide, the thyroid gland eventually escapes this inhibition as the iodide transport system adapts to the higher concentration of iodide by modulating the activity of the sodium-iodide symporter.
- Although iodide is effective at rapidly reducing serum thyroid hormone levels, usually within 7 to 14 days, most patients escape the inhibition and return to hyperthyroidism within 2 to 3 weeks, if no other treatment is given. Therefore, the use of iodide to treat thyrotoxicosis is of limited use, and thus is used only in severe thyrotoxicosis or thyroid storm in combination with thionamide therapy.

Problems with use of iodine
- In the acute setting, if iodine therapy is given before thionamide therapy, new hormone synthesis can be stimulated.
- When planning definitive therapy for thyrotoxicosis after the acute phase of thyroid storm, use of exogenous iodine at any time can predispose a patient to increased surgical risk because of the enrichment of thyroid hormone stores, and can cause postponement of radioiodine ablation until an adequate clearance of the iodine load occurs.

Formulations
- Oral formulations of inorganic iodine include Lugol's solution and saturated solution of potassium iodide. The dosing for these preparations in thyroid storm is 0.2 to 2 g daily, with four to eight drops of Lugol's solution (assuming 20 drops/mL, 8 mg iodine/drop) every 6 to 8 hours and five drops of saturation solution of potassium iodide (with 20 drops/mL, 38 mg iodide/ drop) every 6 hours.
- The oral iodinated contrast agents, iopanoic acid and sodium ipodate, have multiple effects on thyroid hormone in the periphery and within the thyroid gland. These iodinated contrast agents competitively inhibit Types 1 and 2 50-monodeiodinase in the liver, brain, and thyroid, blocking conversion of T4 to T3, resulting in a rapid decrease in T3 and an increase in reverse T3. These iodinated contrast agents have also been found to inhibit binding of T3 and T4 to cellular receptors. In thyroid storm, sodium ipodate (308 mg iodine/500mg capsule) is dosed at 1 to 3 g daily. Usually, iopanoic acid is dosed at 1g every 8 hours for the first 24 hours, followed by 500 mg twice daily.

steroids

- Glucocorticoids are used in the treatment of thyroid storm because:
(i) they have an inhibitory effect on peripheral conversion of T4 to T3. [The clinical relevance of this minor effect is unknown.]
(ii) they treat possible relative adrenal insufficiency. One study found inappropriately normal levels of serum cortisol in a series of subjects with thyroid storm. This study found improved survival in those subjects treated with glucorticoids.
- Dosing of glucorticoids in thyroid storm can be with hydrocortisone 100 mg intravenously every 8 hours, with tapering as the signs of thyroid storm improve.

controlling the cardiovascular manifestations

General
- The cardiovascular changes seen with thyrotoxicosis occur because of the different effects of thyroid hormone on the heart and on systemic vasculature.
- Thyroid hormone decreases systemic vascular resistance by a direct vasodilatory action on smooth muscle and by endothelial release of nitric oxide or other endothelial-derived vasodilators.
- The effect of thyroid hormone on the heart is mediated partly by the genomic effects of T3 binding to specific nuclear receptors. In addition to these genomic effects of T3 in the heart, thyroid hormone also has nongenomic actions, directly altering the performance of sodium, potassium, and calcium channels.

Beta blockade
- In thyroid storm, propranolol is dosed at 60 to 80 mg every 4 hours, or 80 to 120 mg every 4 hours. The onset of action after oral dosing takes place within 1 hour. For a more rapid effect, propranolol can also be administered parenterally, with a bolus of 0.5 to 1 mg over 10 minutes followed by 1 to 3 mg over 10 minutes, every few hours, depending on the clinical context.
- In addition to its effect on beta-adrenergic receptors, propranolol in large doses (greater than 160 mg daily) can decrease T3 levels by as much as 30%. This effect, mediated by the inhibition of 50monodeiodinase, is mediated slowly over 7 to 10 days.
- Esmolol can also be administered parenterally at a dose of 50 to 100 mg/kg/min. Relatively large doses of propranolol are required in the setting of thyrotoxicosis because of the faster metabolism of the drug, and possibly because of a greater quantity of cardiac beta-adrenergic receptors.
- Longer-acting cardioselective beta-adrenergic receptor antagonists such as atenolol and metoprolol may be used also

anticoagulation of AF
- One of the significant cardiovascular complications of thyrotoxicosis is atrial fibrillation, occurring in 10% to 35% of cases. In the largest retrospective study, it appears that thyrotoxic patients who have atrial fibrillation are not at greater risk for embolic events, compared with age-matched patients who have atrial fibrillation due to other causes.
- Standard therapy with warfarin or aspirin is indicated, according to standard guidelines for atrial fibrillation.
- Thyrotoxic patients may require a lower maintenance dose of warfarin than euthyroid patients because of increased clearance of vitamin K-dependent clotting factors

alternative therapies

General:
- Several therapeutic agents used in the treatment of thyrotoxicosis are only considered when the first-line therapies of thionamides, iodide, betablockers, and glucocorticoids fail or cannot be used owing to toxicity.

(i) lithium
- When iodide therapy cannot be used, another agent that can be used to inhibit thyroid hormone release is lithium. Lithium can be also be used when thionamide therapy is contraindicated because of toxicity or adverse reactions.
- Lithium has several effects on the thyroid gland, including directly decreasing thyroid hormone secretion and thereby increasing intrathyroidal iodine content, and inhibiting coupling of iodotyrosine residues that form iodothyronines (T4 and T3).
- In thyroid storm, the dosing for lithium is 300 mg every 8 hours. To avoid lithium toxicity, lithium level should be monitored regularly (perhaps even daily) to maintain a concentration of about 0.6-1.0 mEq/L.

(ii) Reserpine & guanthidine
- Before beta-adrenergic receptor antagonists were used to counteract the peripheral effects of thyroid hormone, the antiadrenergic agents, reserpine and guanethidine, were often used.
- Reserpine is an alkaloid agent that depletes catecholamine stores in sympathetic nerve terminals and the central nervous system.
- Guanethidine also inhibits the release of catecholamines.
- Side effects of these medications include hypotension and diarrhea. Reserpine can also have central nervous system depressant effects.
- These agents are indicated only in rare situations where beta-adrenergic receptor antagonists are contraindicated, and when there is no hypotension or evidence of central nervous system-associated mental status changes
- Dosing for guanethidine in thyroid storm is 30 to 40 mg orally every 6 hours, and for reserpine 2.5 to 5 mg intramuscularly every 4 hours

(iii) Cholestyramine
- an anion exchange resin, has also been used in the treatment of thyrotoxicosis, to help decrease reabsorption of thyroid hormone from the enterohepatic circulation. In several trials, cholestyramine therapy, in combination with methimazole or propylthiouracil, caused a more rapid decline in thyroid hormone levels than standard therapy with thionamides alone. In these trials, cholestyramine was dosed at 4 g orally four times a day.
- The effect of cholestyramine is generally minimal and it should not be administered at the exact same time as other medications because it may inhibit their absorption. On the other hand, cholestyramine is not expected to be associated with significant adverse effects.

(iv) plasmapheresis
- When clinical deterioration occurs in thyroid storm, despite the use of all of these medications, removal of thyroid hormone from circulation would be a therapeutic consideration. Plasmapheresis, charcoal hemoperfusion, resin hemoperfusion, and plasma exchange have been found to be effective in rapidly reducing thyroid hormone levels in thyroid storm.

supportive care

- Supportive care is an important part of the multisystem therapeutic approach to thyroid storm.
- Because fever is very common with severe thyrotoxicosis, antipyretics should be used; paracetamol is the preferable choice. Salicylates should be avoided in thyrotoxicosis because salicylates can decrease thyroid protein binding, causing an increase in free thyroid hormone levels. External cooling measures can also be used.
- Fluid loss and dehydration are also common in severe thyrotoxicosis. The fluid losses could result from the combination of fever, diaphoresis, vomiting, and diarrhea.
- Intravenous fluids with dextrose (isotonic saline with 5% or 10% dextrose) should be given to replenish glycogen stores. Patients should also receive multivitamins, particularly thiamine, to prevent Wernicke's encephalopathy, which could result from the administration of intravenous fluids with dextrose in the presence of thiamine deficiency.

- Treating the precipitating cause of thyrotoxicosis is particularly important, considering that the most common precipitant is thought to be infection. If a precipitating factor were not readily apparent, a vigorous search for an infectious source would be warranted in the febrile thyrotoxic patient; this would be done with blood, urine, and sputum cultures, and a chest radiograph. Generally, however, empiric antibiotics are not recommended without an identified source of infection.