When Good Hormones Go Bad: Acute Management of Endocrine Emergencies

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Disclosure

All planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.
Objectives

• Describe the management of endocrine emergencies in the Emergency Department with emphasis on potential pharmacotherapy interventions

• Evaluate potential strategies to ensure appropriate implementation of expert recommendations in a busy Emergency Department

• Determine effective strategies for optimizing patient outcomes and minimizing the risk of medication errors
THE RIGHT AMOUNT OF ‘-ROIDS’

A review of adrenal emergencies and treatment options
Patient Case

You are the EM Clinical Pharmacy Specialist and you walk in to start your tour and are told that they need you to do a procedural sedation in Bed 4

- You are told the following:
  - 20yo pregnant female presents with a right shoulder dislocation s/p falling at clinic appointment after standing
  - PMH: bilateral shoulder dislocations
  - Vitals: BP 130/90; HR 78; RR 12
Patient Case

• Knowing that she has had this done before, but only at other hospitals, you go to ask what sedatives have worked in the past
• Patient states that previous attempts to put her shoulder back in place have used propofol
  – "I take it like a champ they say!"
• Decision is made to do a procedural sedation utilizing fentanyl and propofol
Patient Case

- Patient is administered the following:
  - Fentanyl 50 mcg and Propofol 0.5 mg/kg
  - Propofol 0.25 mg/kg x 2
  - Propofol 0.75 mg/kg x 2 and fentanyl 50 mcg
- After finally achieving sedation prior to shoulder manipulation, patient’s BP is noted to be 80/40 mmHg
- Probably too much propofol of course...until you see the box of hydrocortisone in her purse at bedside...
Hypothalamic-Pituitary-Adrenal Axis

Stress → Hypothalamus → Corticotropin Releasing Hormone → Anterior Pituitary → Adrenocorticotropic Hormone → Adrenal Cortex

Cortisol: Secretes
Aldosterone: Secretes

Inhibits
Adrenal Insufficiency

• Primary (Addison Disease)
  – Autoimmune disorder-80%
  – Tuberculosis and human immunodeficiency virus are common infectious causes

• Secondary
  – Integrity of the HPA axis is lost because of pituitary disease
  – Secretion of ACTH is diminished, cortisol production reduced and adrenal atrophy ensues
  – No hyperpigmentation, not hyperkalemic, hypernatremic, or hyponatremic

• Tertiary
  – Hypothalamic disease
  – CRH secretion is diminished leading to minimal ACTH and cortisol production
  – Secondary to long-term glucocorticoid therapy
### Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Primary</th>
<th>Secondary</th>
<th>Tertiary</th>
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</thead>
<tbody>
<tr>
<td>Serum cortisol</td>
<td>Low</td>
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<tr>
<td>ACTH</td>
<td>High</td>
<td>Normal/Low</td>
<td>Normal/Low</td>
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<tr>
<td>ACTH Stimulation</td>
<td>No effect</td>
<td>Restores function</td>
<td>Restores function</td>
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<tr>
<td>CRH Stimulation</td>
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<td>Absent</td>
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ACTH: Adrenocorticotropic hormone; CRH: Corticotrophin-releasing hormone
## Differentiation

<table>
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<tr>
<th>Signs/Symptoms</th>
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<tr>
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<td>Hyperpigmentation</td>
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<tr>
<td>Aldosterone Deficiency</td>
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<td>Potassium</td>
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<td>Glucose</td>
<td>Mild Hypoglycemia</td>
<td>Marked Hypoglycemia</td>
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Adrenal Crisis

• Primary 47%, Secondary 35%
• Precipitating factors:
  – Fever 15-24%
  – Gastrointestinal Illness 22-33%
  – Surgery 7-16%
  – Drugs: ketoconazole, etomidate
Signs & Symptoms of Adrenal Crisis

- Hypotension/shock: 90%
- Fever: 66%
- Abdominal/flank/back/chest pain: 86%
- Anorexia/nausea/vomiting: 47%
- Confusion/disorientation: 42%
Acute Presentation

• Sudden worsening of symptoms plus hemodynamic instability
  – Inability to support stress in the setting of infection, trauma, or surgery
• Result is mental status changes, tenuous vital signs, and laboratory derangements
  – Hyponatremia, hypoglycemia, hypercalcemia, hyperkalemia and metabolic acidosis
First Steps

• Obtain random cortisol and adrenocorticotropic hormone levels

• Cosyntropin stimulation tests can be performed for confirmation
  – Should not delay treatment
Testing for Adrenal Insufficiency

• In a state of stress, a random cortisol should be sufficient
  – >20 mcg/dL implies adequate function
  – < 4 mcg/dL is suggested to be deficient
• Cosyntropin (ACTH) is the preferred test
  – Tests the ability of the adrenal cortex to respond specifically
  – Baseline cortisol, 1 mcg of cosyntropin, repeat cortisol
  – Appropriate adrenal response:
    • A cortisol level of 20-25 mcg/dL
    • An increase of >9 mcg/dL from baseline
Treatment

- Fluid resuscitation
- Electrolyte optimization
- Identify precipitating cause
- Stress dose steroid administration
  - Hydrocortisone 100 mg IV/IM q8hrs
  - Dexamethasone 4 mg
    - Does not contain adequate mineralcorticoid activity
    - Does not affect cosyntropin test
  - Continue every six hours x 24 hrs or until patient returns to baseline

Patient Case:
What are your next steps?

A. Stop procedure and allow the propofol to wear off
B. Administer 1 liter normal saline
C. Administer hydrocortisone 100 mg x 1
D. Administer fludrocortisone 50 mcg x 1
Pheochromocytoma

• Neuroendocrine tumors that secrete excess catecholamines and cause life-threatening hypertension

• The inner zone of the adrenal gland: medulla
  – Consists of cells that produce catecholamines (norepinephrine, epinephrine, and dopamine)
  – Released in response to sympathetic stimulation
Presentation

• Classically present as ‘spells’
  – Headaches (82%), palpitations (48%), hypertension (98%)
    • Monthly, weekly, daily, or multiple times per day
    • Attacks build over a few minutes and then fade over a short time
• Neurologic symptoms secondary to cerebrovascular accidents
• Can present as severe abdominal pain, nausea, and vomiting
• Multisystem crisis is the most severe presentation
• Any patient presenting with acute hypertension and tachycardia should be considered at risk
  – Especially if young with no comorbidities

Precipitating Factors

- Oncologic causes
- Exercise
- Abdominal pressure
- Pregnancy
  - 65% is undiagnosed (generally not seen until 20 weeks)
- Drugs
  - Glucagon, naloxone, metoclopramide, ACTH, imipramine, glucocorticoids

Pharmacotherapy Management

• No consensus

• Alpha-adrenergic-receptor blockade
  – Phentolamine or Phenoxybenzamine
  – Prazosin, terazosin, doxazosin

• Beta-blockers are included to treat reflex tachycardia
  – Should not be started before alpha blockade
  – Cardioselective and noncardioselective

• Nitroprusside, nitroglycerin, magnesium sulfate

• Bridge to surgery
  – Only curative measure
Phenoxybenzamine

- Non-competitive alpha-1/alpha-2 antagonist
- 10 mg TID, increasing to a maximum dose of 240 mg/24 hrs
  - Seldom need >40 mg TID
- Titrate every 48 hrs until blood pressure control achieved
- After this tachycardia may be present
  - Propranolol 40 mg TID

You made that drug up!

- 20 yr review of 100 patients that underwent resection
- Use of phenoxybenzamine dose was a significant predictor of improved intraoperative stability (p=0.01)
  - Was given 2-7 days prior to admission and then continued for 5-10 days while in the hospital
  - Beta-blockade was added for persistent rate >120 beats/min
- Magnesium may have a role
Clinical Pearls

• Alpha blockade should always precede beta blockade
• Side effects
  – Postural hypotension, nasal stuffiness, drowsiness, and dilutional anemia
• Calcium channel antagonists are not recommended empirically
• Labetalol is not recommended secondary to its greater beta blockade compared to its alpha blockade

What steroid does not interfere with a cosyntropin stimulation test?

A. Dexamethasone
B. Hydrocortisone
C. Methylprednisolone
D. Fludrocortisone
Key Takeaways

- Key Takeaway #1
  - Evaluating patients for adrenal insufficiency in the ED requires a thorough understanding of the clinical signs and symptoms

- Key Takeaway #2
  - Pheochromocytoma is a rare but life-threatening presentation that requires the development of an emergent plan

- Key Takeaway #3
  - The proactive development of treatment pathways for these emergencies will allow for more expeditious care
BIG, LARGE, AND IN CHARGE: THE THYROID

A review of thyroid emergencies and available treatment options
Thyroid Hormones

Thyroid hormones affect nearly every organ system

- ↑ Lipogenesis and lipolysis
- ↑ Osteogenesis and osteolysis
- ↓ Systemic vascular resistance
- ↑ Cardiac output and contractility
Thyroid Hormones

• Neither protein nor steroid-based
• Incorporate iodine
• Triiodothyronine (T3)
• Thyroxine (T4)

• Thyroid stimulating hormone (TSH)
• T3 and T4 stored in the thyroid gland
  – In combination with thyroglobulin
Assessing the Thyroid Function

• 80% of T3 is converted from T4 peripherally
  – 20% is secreted by the thyroid
  – T3 has greater biologic activity
• Free thyroid concentrations used to determine thyroidal state
  – Total concentrations not useful
• TSH is a sensitive marker for thyroid function
  – Small changes in free hormone drastically alter TSH secretion
Thyroid Function Tests

- **Hypothyroidism**
  - TSH: ↑
  - T4 and T3: ↓

- **Hyperthyroidism**
  - TSH: ↓
  - T4 and T3: ↑

<table>
<thead>
<tr>
<th></th>
<th>TSH (mIU/L)</th>
<th>T4 (ng/dL)</th>
<th>T3 (ng/dL)</th>
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<tr>
<td>Hyperthyroid</td>
<td>Decrease</td>
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<tr>
<td>Hypothyroid</td>
<td>Increase</td>
<td>Decrease</td>
<td>Decrease</td>
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</table>
Thyroid Tests in the Critically Ill

- Nonthyroidal illness syndrome
  - Euthyroid sick syndrome

- Low thyroid levels in setting of critical illness
  - Reverse T3
  - Adaptive or protective state

- Assessing thyroid levels in critical illness
  - Multiple needed throughout the clinical course
  - TSH levels >20 mcgIU/mL indicative of primary hypothyroidism

Clinical Pearls: Thyroid Function Tests

- TSH is a sensitive marker of change in thyroid function
- Important to assess TSH in combination with free T4
- Important to identify primary thyroid disorders in critical illness
Hypothyroidism
Hypothyroidism

- 10 times more common in women
  - Most age >60 years
- Challenge to emergency medicine physicians
  - Significant portion asymptomatic
  - Vague and mimics other disease states

Physical exam
- Pale, cool skin
- Hypothermia
- Edema
  - Non-pitting periorbital edema
  - Myxedema
- Bradycardia

Thyroid Hormones and the Heart

• T3 stimulates calcium influx into cells and helps to regulate cellular potassium fluctuations

• Thyroid hormones
  – Reduces peripheral vascular resistance
  – Increases cardiac output and heart rate
  – Increases systolic blood pressure
Presentation of Myxedema Coma

- Most common presentation
  - Age > 60 years (80%)
  - Female
  - History of long-standing hypothyroidism
  - Present in winter months

- Mortality rate up to ranging from 15-20%
  - As high as 80% prior to 1960s

- Complications
  - Sepsis
  - Aspiration pneumonia

Symptoms of Myxedema Coma

- Profound hypothermia (80°F/27°C)
- Comatose state
- Profound bradycardia
- Neurologic findings
  - Cerebellar signs
  - Poor memory
  - Abnormal EEG
- Decreased respiratory drive

Reduced T4

Reduced Intracellular T3

CNS
- Altered mental status

Cardiovascular
- Decreased inotropy and chronotropy
  - Decreased cardiac output
  - Increased vasoconstriction

Fluid Balance
- Increased vascular permeability
  - Increased water retention

Respiratory inefficiency
- Decreased sensitivity to hypoxia

Cerebral anoxia
- Decreased blood pressure
- Shock

Hypothermia

Hypoxia
Reduced T4

Reduced Intracellular T3

CNS
Altered mental status

Decreased thermogenesis
Hypothermia

Cardiovascular
Decreased inotropy and chronotropy

Fluid Balance
Increased vascular permeability
Increased water retention

Decreased cardiac output
Increased vasoconstriction
Decreased blood pressure

Cerebral anoxia
Decreased inotropy and chronotropy

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Altered mental status

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Cerebral anoxia
Decreased inotropy and chronotropy

Respiratory inefficiency
Decreased sensitivity to hypoxia

Ultimately Resulting in Coma
Management

• Supportive care
  – Fluid resuscitation
  – Mechanical ventilation

• Thyroid hormone
  – Definitive treatment
  – Baseline TSH and free T4
  – Risk of precipitating cardiovascular events

• Glucocorticoid supplementation
Strategies for Thyroid Replacement

- T4 Alone
- T3 Alone
- T4 + T3 Combination

Arch Intern Med. 1964;113(1):89-96
T3 and T4 in Myxedema Coma

- No randomized trials comparing T3, T4, or a combination of the two
- IV thyroxine (T4) has remained the standard of care since 1960s
  - Prior to this, mortality approached 80-90%
- High dose versus low dose thyroid hormone
  - Safety versus efficacy
T3 and T4 in Myxedema Coma

• Thyroxine (T4) alone
  – 4 mcg/kg or standardized to 200-500 mcg IV of T4
    • Increases peripheral pool
    • Slow conversion to T3 in periphery reducing cardiovascular effects
    • Consider severity of clinical presentation when deciding dose
  – 50-100 mcg/d IV thereafter until enteral access is obtained

T4 in Myxedema Coma

• Holvey et al
  – Case series of 7 patients
  – Treatment of myxedema coma with IV thyroxine
  – 400-500 mcg IV loading dose
  – Resolution of symptoms
    • 6-12 hours
  – Regained consciousness
    • 24-36 hours
  – No adverse events correlated to drug therapy

Arch Intern Med 1964;113:139–46
Adverse Effects of Thyroxine

- Yamamoto et al
- Retrospective evaluation
- 8 patients treated for myxedema coma over 18 years
- Conducted a MEDLINE database search (n=87)
- Identify risk factors for fatal outcome with thyroid hormone dose
  - High (≥ 500 mcg/day T4 or ≥ 75 mcg/day T3) versus low-dose

Thyroid 1999;9(12):1167–74
Yamamoto et al Cont.

- Results associated with a fatal outcome
  - Greater age, cardiac complications, high-dose T4, and high-dose T3

- Application to clinical practice
  - Doses of ≤ 500 mcg IV T4 are safe for first bolus dose
    - ≥ 500 mcg/d given enterally have a more favorable outcomes compared to IV
    - Lower doses in elderly patients may be beneficial
      - Lower potential for cardiovascular complications

Thyroid 1999;9(12):1167–74; Arch Intern Med 1964;113:89–96
What About T3?

• Proponents of T3 monotherapy
  – Increased biologic activity
  – Quicker onset of action

• T3 Dosing
  – 10-20 mcg IV x 1
  – 10 mcg IV every 4 hours x 24 hours
  – 10 mcg IV every 6 hours x 24-48 hours

What About T3?

• High doses of T3 have been associated with higher rates of mortality
  – Cardiac arrhythmias
  – Myocardial infarction
• Cost compared to T4
Combination Therapy

• Combination T4 + T3
  – 200-300 mcg IV T4, 100 mcg/d thereafter + 10 mcg IV T3 every 8-12 hours
  – Thought to be better physiologic balance
• Cost compared to either alone
• Unnecessary and no advantages to either alone

Glucocorticoids

• Thyroid hormone supplementation can cause or worsen adrenal insufficiency
  – Increased metabolism of cortisol

• Stress doses should be used with thyroid hormone
  – 100mg IV hydrocortisone every 8 hours
    OR
  – 50mg IV hydrocortisone every 6 hours

• Baseline random cortisol
Clinical Pearl

• Intravenous thyroxine (T4) is the standard of care
  – 200-500 mcg IV or orally initially followed by 50-100 mcg IV daily
• Combination therapy is unnecessary and costly
• Stress dose steroids are necessary part of treating myxedema coma
Hyperthyroidism
Hyperthyroidism

• Increased metabolism
  – Grave’s disease
    • Developed countries
  – Toxic multinodular goiter (TMNG)
  – Toxic adenoma (TA)

• Decreased metabolism
  – Thyroiditis

• T3/T4 ratio
  – >20: Increased metabolism
  – <20: Decreased metabolism
Thyrotoxicosis

- TSH
  - Suppressed in most cases
- Free T4
  - Elevated 95% of cases
- Isolated free T3 elevations
  - Elevated in only 5% of cases

Proposed physiologic mechanism
- Elevated intracellular levels of T3 and T4
  - Suppress thyrotropin
  - Increase in target β-adrenergic receptor density
Symptoms of Thyrotoxicosis

- Heat intolerance
- Palpitations
- Chest pain
- Shortness of breath
- Nervousness
- Weight loss
- Hair loss
- Enlargement of the thyroid
Thyroid Storm

- Graves’ disease most common underlying cause
- Mortality ranges from 20-50%
- Occurs in <10 % of those with thyrotoxicosis
- Transitioning from thyrotoxicosis to thyroid storm
  - Subjective
  - No defined serum hormone cutoff
  - Precipitating event

Thyroid Storm: Diagnostic Criteria

- Burch and Wartofsky point system
- Degree of dysfunction
  - Thermoregulatory
  - Cardiovascular
    - Tachycardia, atrial fibrillation, or heart failure
  - Central nervous system
    - Agitation or psychosis
  - Gastrointestinal-hepatic
    - Nausea or vomiting, or diarrhea
<table>
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<th>Diagnostic Parameters</th>
<th>Score</th>
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<tr>
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<td>Severe (seizures, coma)</td>
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<td>Severe (pulmonary edema)</td>
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<td>20</td>
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</table>

| Total Scores          |       | Precipitating event   |       |                       |       |
| Thyroid Storm 45 <    |       | Storm unlikely 25 >    |       | Absent                | 0     |
| Impending Storm 25-44 |       | Present               | 10    |                       |       |
Management

• Supportive care
• Antithyroid medications
• Radioactive iodine
• Drugs to block peripheral effects of thyroid hormone
  – β-adrenergic antagonists
• Thyroidectomy
  – Most invasive intervention
  – Highest risk of complication
Antithyroid Medications

- Thionamides
  - Propylthiouracil (PTU)
  - Methimazole (MMI)

- 30-40% go into remission
  - Have little effect on preformed hormone release

- Mechanism of action
  - Prevents synthesis of T4
  - Inhibit incorporation of iodine into thyroglobulin
  - PTU inhibits conversion of peripheral T4 to T3

# Antithyroid Medications

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<tr>
<th>Methimazole</th>
<th>Propylthryouracil</th>
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<tbody>
<tr>
<td>• Initial: 10-20 orally mg every 4-6 hours</td>
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<tr>
<td>• Maintenance: 10-30 mg orally once daily</td>
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<tr>
<td>• Antithyroid effects: 12-18 hours</td>
<td>• Initial: 100-250mg orally every 4-6 hours</td>
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<tr>
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<td>• Maintenance dosing: 50-200 mg daily</td>
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<td></td>
<td>• Antithyroid effects: 24-36 hours</td>
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</table>
Nakamura et al

- Treatment arms
  - MMI 30mg/d versus MMI 15mg/d versus PTU 300mg/d

- Results
  - Reductions in T4
    - 52.7% (MMI 30), 38.4% (PTU 300), and 36.7% (MMI 15)
    - MMI 15 mg/d significantly less effective than MMI 30 mg/d
  - AST and ALT
    - More than twice upper limit of normal 26.9% (PTU 300) versus 6.6% (MMI 30)
  - MMI in higher doses is more appropriate for severe hyperthyroidism or Graves’ disease

J Clin Endocrinol Metab 92: 2157–2162, 2007
Radioactive Iodine

- Most common treatment option for Grave’s disease
- Thyroid function tests return to normal in 2-4 months
- Hypothyroidism develops after 4-12 months
  - Lifelong therapy with L-thyroxine
- Contraindicated in pregnancy
Blocking Preformed Hormone

- Iodine preparations
- Lithium Carbonate
- Inhibiting conversion of T4 to T3
- Inhibiting adrenergic stimulation
Blocking Preformed Hormone

- Iodine preparations (Lugol’s iodine, Saturated solution of potassium iodide (SSKI))
  - Decreased iodine transport, organification, and secretion by the gland
  - Given 1-2 hours after first dose of MMI/PTU

- Lithium carbonate
  - Inhibits thyroidal iodine uptake and secretion of hormone
  - 300 mg every 6 hours
  - Iodine allergies
  - Goal serum concentration of 1 mEq/L (mmol/L)

Inhibiting Peripheral Hormone Action

- Inhibit peripheral conversion of T4 to T3
  - Propylthiouracil
  - Iopanoic acid
  - Propranolol
β-adrenergic antagonists

- Antagonize sympathetic hyperstimulation
- Propranolol
  - Oral: 60-80 mg every 4-6 hours
  - Intravenous: 1-3 mg every 4-6 hours
- Esmolol
  - 50 mcg/kg bolus
  - Continuous infusion

Corticosteroids

• Thyrotoxicosis and thyroid storm accelerates
  – Metabolism of cortisol
  – Production of cortisol
• Results in normal to increased levels of circulating cortisol
• Adrenocortical reserve can be diminished
  – Normal serum cortisol levels may indicate need for stress dose steroids
Clinical Pearl

- Drug of choice for hyperthyroidism or thyroid storm
  - MMI faster onset of antithyroid effect
  - MMI better patient compliance
  - PTU preferred in pregnancy
  - Avoid PTU in pediatric patients
- Beta blockade
  - Inhibit adrenergic stimulation while antithyroid medications take action
Patient Case

• Arthur is a 21yo male presents to the ED with 4 day history of sore throat, fever, heat intolerance, palpitations, diaphoresis, tremors, mild diarrhea, mildly agitated
  – 20 lb weight loss over 3 months
  – Diagnosed with Graves’ disease (GD) at age 15 years
    • Refused surgery or radioactive iodine (RAI)
    • Stopped taking antithyroid medication ~1 year ago

• Temperature: 99°F
• SBP 150 mmHg; HR 150 bpm
  – No signs of heart failure or atrial fibrillation
• Laboratory values
  – TSH <0.01 mcgIU/mL
  – T4 >8 ng/dL
  – Random cortisol 7.9 mcg/dL
    • Normal 3-14 mcg/dL
Based on initial presentation, what is Arthur’s diagnosis?

A. Thyrotoxicosis
B. Thyroid Storm
C. Myxedema Coma
D. Sepsis
At the cellular level, which thyroid hormone responsible for the most biologic activity?

A. Thyroxine (T4)
B. Triiodothyronine (T3)
C. Reverse T3 (rT3)
D. Thyroid stimulating hormone (TSH)
Given the diagnosis of thyroid storm, what would you recommend as essential initial therapies?

A. Radioactive iodine, propranolol
B. Metoprolol tartrate, PTU
C. Propranolol, MMI, corticosteroids
D. Supportive care, SSKI, thyroidectomy
Key Takeaways

• Key Takeaway #1
  – Diagnosing primary thyroid disorders in the ED requires evaluating TSH in conjunction with clinical signs and symptoms

• Key Takeaway #2
  – Myxedema coma is commonly mistaken for other clinical diagnoses, which mimic other conditions

• Key Takeaway #3
  – Pituitary apoplexy is often a surgical emergency necessitating rapid diagnosis and management
When Good Hormones Go Bad: Acute Management of Endocrine Emergencies

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