

Toxic Fever

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Case 1

- 23 y/o female brought to ED with AMS
- PMH: depression on Rx
- Exam: hyper-reflexia
- VS: HR 110; BP 140/95; RR 20; 99% RA; T 40

- Differential diagnosis?
- Causes of high temperature?
- Management?

Objectives

- Review basic principle of thermoregulation
- Review common causes of toxin-induced hyperthermia
- Understand how to manage toxin-induced hyperthermia

TABLE 17-1. Toxic Syndromes

Group	Vital Signs				Mental Status	Pupil Size	Peristalsis	Diaphoresis	Other
	BP	P	RR	T					
Adrenergic (α , β) agents	↑	↑	↑	↑	Altered	↑	↑	↑	Tremor
Anticholinergic agents	±	↑	±	↑	Altered	↑	↓	↓	Dry mucous membranes, flush, urinary retention
Cholinergic (muscarinic, nicotinic) agents	±	±	—	—	Altered	±	↑	↑	Salivation, lacrimation, urination, bronchorrhea, fasciculations, bradycardia
Opioids	↓	↓	↓	↓	Altered	↓	↓	—	Hyporeflexia
Withdrawal of opioids	↑	↑	—	—	Normal	↑	↑	↑	Nausea, vomiting, hyperactivity, rhinorrhea, piloerection
Sedative-hypnotics or ethanol	↓	↓	↓	±	Altered	±	↓	—	Hyporeflexia
Withdrawal of sedative-hypnotics or ethanol	↑	↑	↑	↑	Altered	↑	↑	—/↑	Nausea, tremor, seizures

↑ = increases; ↓ = decreases; ± = variable; — = change unlikely



Thermoregulatory Principles



Overview

- Methods of heat transfer
- Physiology of thermoregulation
- Drug effects on thermoregulation
- Hyperthermia

Methods of Heat Transfer

- Radiation
- Conduction
- Convection
- Evaporation

Physiology of Thermoregulation

- Thermoregulation

- The complex process that maintains hypothalamic temperature within the range of 36.6-37.4 degrees Celsius

- Four areas of thermoregulation

- Hypothalamus
- Medullary reticular formation
- Spinalthalamic tract
- Skin

Physiology of Thermoregulation

- Neurotransmitters involved in thermoregulation
 - Exact mechanism is poorly understood
 - Serotonin
 - Norepinephrine
 - Acetylcholine
 - Dopamine
 - Prostiglandins
 - β -endorphins
 - ACTH
 - TSH
 - α -melanocyte stimulating hormone

Drugs Effect on Thermoregulation

- Impaired heat loss
- Myocardial depression
- Hypothalamic depression
- Impaired behavioral response
- Uncoupled oxidative phosphorylation
- Agitation, Seizure, Rigidity
- Dystonia
- Withdrawal

Drugs That Effect Thermoregulation

- Hyperthermia (NASA):
 - Neuroleptic malignant syndrome, nicotine
 - Antihistamines, Alcohol withdrawal
 - Salicylates, sympathomimetics, serotonin syndrome
 - Anticholinergics, antidepressants, antipsychotics

■ Thomson T. Emerg Med Clin N Am 25 (2007) 249–281

Drugs That Effect Thermoregulation

■ Hypothermia (COOLS):

- C arbon monoxide
- O pioids
- O ral hypoglycemic, insulin
- L iquor (alcohols)
- S edative-hypnotics

- Thombson T. Emerg Med Clin N Am 25 (2007) 249–281

Factors That Effect Thermoregulation

- Old age
- CNS depression
 - Hypothalamic dysfunction, Infection, ICB, Stroke
- Endocrine
 - DKA, Hyperosmolar coma, Hypothyroid
- Environmental
- Hepatic failure
- Immobilization
- Poor nutrition
- Sepsis
- Uremia

Hyperthermia

- Definition of heatstroke
 - Core temp > 41.1° C
 - Neurologic disturbance
 - Seizure, delirium, coma, agitation, psychosis
 - Patients may maintain ability to sweat

Heatstroke

- Nonexertional

- Occurs during heat waves

- Exertional

- Due to increased motor activity

- Exercise, seizure, agitation

- Precipitating factors

- Fatigue, sleep loss, poor physical conditioning, febrile illness, dehydration, obesity

Heatstroke

- Differential diagnosis
 - Primary hypothalamic lesion
 - Intracerebral bleed
 - Alcohol and sedative-hypnotic withdrawal
 - Seizure
 - Drugs
 - Serotonin syndrome
 - Malignant hyperthermia
 - Neuroleptic malignant syndrome

Heatstroke

- Treatment
 - Supportive care
 - Rapid Cooling
 - IV Hydration
 - Control the cause
 - Continuous monitoring

Case 2

- CC: AMS
- HPI: 50 y/o male h/o schizophrenia had medications changed from Chlorpromazine to Risperidone. Dose escalated over the week to control his symptoms. Has become altered from baseline.
- PE: hyperthermic, agitated, rigid
 - Diagnosis? Why?

Case 2: NMS

- Neuroleptic malignant syndrome
 - “Malignant” = previously high mortality
 - Rare (<2.0%), idiosyncratic
 - Men>>women
 - Any dopamine antagonists
 - Usually first 1-2 weeks drug initiation, drug change, dose change, but anytime possible

Case 2: NMS

- Clinical diagnosis
- Exposure to dopamine antagonists + Tetrads:
 - Altered mental status
 - Muscular rigidity
 - Autonomic instability
 - Hyperthermia
 - Altered dopamine response in hypothalamus, agitation, muscle rigidity
 - Correlates with mortality, severe $>40^{\circ}\text{C}$

Case 2: NMS

- Poorly understood
- D2 receptor blockade
 - **Nigrostriatum** → muscle rigidity, parkinsonism
 - **Thermoregulatory center** → hyperthermia
 - **Mesocortical and mesolimbic** → AMS
 - **Peripheral sympathetic nerves, vascular smooth muscle** → autonomic dysfunction

Case 2: NMS

- Antipsychotic agents with strongest antidopaminergic effects that more likely to cause NMS:
 - Phenothiazines (Chlorpromazine, Prochlorperazine)
 - Butyrophenones (Haloperidol, Droperidol), and other typical agents.

Case 2: NMS

- Atypical agents, such as olanzapine, have been associated with NMS, but these agents as a class are much less likely to be associated with the syndrome

Case 2: NMS

- Risk Factors:
 - Agitated, dehydrated, large # IM injections
 - Rate of increase of dose, not actual dose
- May be prolonged course
- Complications: rhabdo, metabolic acidosis

Treatment

- Rule out other medical causes
- Stop offending agent
- Agitation - benzos, paralysis
- Muscle rigidity - benzos, paralysis
- Autonomic instability – pressors
- Hyperthermia - benzos, paralysis

Treatment

- Dopamine agonists (bromocriptine)
 - Oral medication
 - Takes 24 hrs to work
- Dantrolene
 - Inhibits Ca^{+2} release from sarcoplasmic reticulum in skeletal muscles
 - Muscle relaxation
 - Take 24 hrs to work
- Anticholinergic agents not effective

Case 3

- 23 y/o female presented with AMS
- No h/o overdose
- Was just started on citalopram 2 days prior presentation
- VS HR 115; BP 140/50; T 37.9; 99%; RR 15
- Exam: rigid lower limbs
 - Differential diagnosis?
 - Management?

Serotonin Syndrome

■ Pharmacology:

- SS results from excessive stimulation of central and peripheral nervous system serotonin receptors namely:
 - 5-HT_{1A} and 5-HT_{2A}
 - It may occur with drug interactions, therapeutic dosing, or deliberate self-harm

Serotonin Syndrome

- 4 ways to account for excessive serotonin activation at 5-HT_{1A} and 5-HT_{2A} receptors:
 - **Decreased serotonin breakdown** (MAOIs)
 - **Decreased serotonin reuptake** (SSRIs, cocaine, dextromethorphan, meperidine, SNRIs)
 - **Increased serotonin precursors/agonists** (L-tryptophan, LSD)
 - **Increased serotonin release** (amphetamines, ecstasy, buspirone, lithium)

Serotonin Syndrome

■ *Triad*

- Altered mental status,
- Neuromotor rigidity
- Autonomic disturbances

Serotonin Syndrome

- Diagnostic Criteria for the Serotonin Syndrome
 - Criteria *A, B, and C must each be satisfied*
 - A. Occurs after the addition of a known serotonergic agent to an established medication regimen or an increase in the dose of a serotonergic agent
 - B. Other causes ruled out
 - C. A neuroleptic agent had not been started or increased in dosage before the onset of the signs and symptoms

Epidemiology

- Rarely occurs in overdose of SSRI's
- Can occur from a single dose
- Most commonly occurs from adding another Serotonin degradation inhibitor to a current (i.e. SSRI and MAOI-a)

Treatment

- Primary- Supportive care
- Benzo's for rigidity and agitation
- Aggressive external cooling
- Cyproheptadine – PO only

Other Treatments

- Propranolol

- Presumed 5-HT₁ antagonist
- Worked well in animals

- Methylsergide

- Non-selective 5-HT antagonist
- Worked in animals, used in humans with only anecdotal reports

SS Observation criteria

- Patients with suspected SS should be evaluated in a healthcare facility
- Mild cases that resolve with benzodiazepines and supportive care may be observed in a monitored setting until asymptomatic

SS Outcome

- Most symptoms resolve within 24 hours
- No long term sequela as long as there are no complications from the acute event (i.e. prolonged hyperthermia)
- Be cautioned of the long $t_{1/2}$ of some SSRI's (Fluoxetine) and potential for recurrence

Case 4



- 65 y/o male brought from home for AMS 3 days. Has schizophrenia, but more agitated and altered. Recent URI. Given over the counter cold medications
- Rx: chlorpromazine, benztropine, Benedryl cold and sinus x 1 week
- PE: febrile, tachycardiac, hypertensive, agitated, big pupils, dry mucous membranes, normal reflexes
- Diagnosis?

Case 4 Mad as a Hatter



- Anticholinergic toxidrome
 - Mad as a Hatter, Dry as a Bone, Seizing like a squirrel, Tacky as a Pink Flamingo...
- Review the medication list
 - Anticholinergic stacking: Chlorpromazine, Diphenhydramine (Benedryl)

Anticholinergic Toxidrome Treatment



- Good supportive care
 - Agitation – benzodiazapines, paralyze
 - Seizures – benzodiazapines, paralyze
 - Hyperthermia – benzodiazapines, paralyze
- Physostigmine
 - Reversible cholinesterase inhibitor
 - Risk of seizures & dysrhythmias

Anticholinergic toxidrome



- Some antipsychotics have high affinity for central muscarinic receptors
- Check medication list for drug-drug interactions

Summary

- Hyperthermia can be induced by different toxins through different mechanism
- High index of suspicion is a key for reaching a timely diagnosis



Thank You

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