Drug-Induced Fever & Hyperthermia in Critically Ill Patients

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Disclosures

- I have no actual or potential conflict of interest in relation to this presentation.

Objectives

- Understand the pathophysiology of fever and hyperthermia
- Differentiate between the mechanisms of drug fever
- Identify the clinical features associated with drug fever
- Understand treatment of drug fever

My patient has a fever…

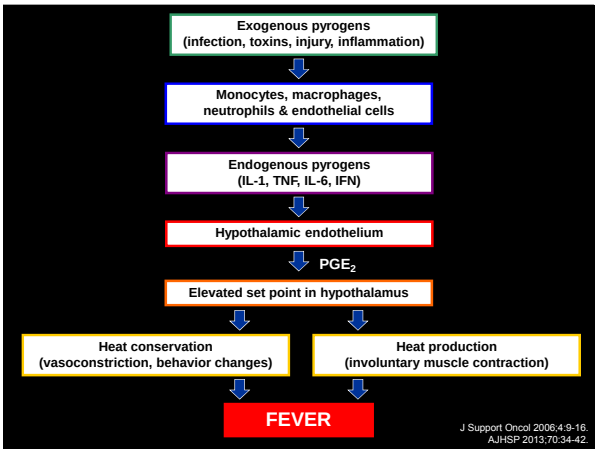
It's late Saturday night and you are taking care of patient M.M., an 86 year old male admitted 7 days ago with septic shock secondary to MSSA pneumonia. He has had difficulty weaning from the ventilator but is hemodynamically stable off all vasopressors. His medications include aspirin, cefazolin, enoxaparin, famotidine, fentanyl, docusate, furosemide, insulin, and simvastatin. He has been afebrile for 48 hours, but his temperature tonight was elevated at 101.6°F. A repeat temperature is 102.1 °F. What would you do to address this patient's elevated temperature?

A. Obtain blood cultures.
B. Broaden antibiotics to piperacillin/tazobactam, vancomycin, and tobramycin.
C. Treat the patient's fever with acetaminophen.
D. Discontinue cefazolin. This fever is definitely drug-induced.

Definitions

- **Normal body temperature**
  - 98.6°F (37 °C)
- **Fever**
  - >101°F (38.3°C)
- **Fever vs. Hyperthermia**
  - Fever: elevated body temp caused by increase in hypothalamic set point
    - Normal physiologic response
  - Hyperthermia: unregulated elevation in body temp that occurs despite a normal hypothalamic set point

Clin Infect Dis 2011;52(4):e56-e93.
Crit Care Med 2013; 41:580–637.
Crit Care Med 2008;36:1330-49
Crit Care Med 2010; 38(6 Suppl): S244-52.



J Support Oncol 2006;4:9-16.
AJHSP 2013;70:34-42.

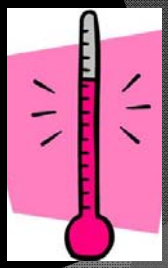
Causes of Fever in Critically Ill Patients

- **Infectious**
  - Catheter-related blood stream infections
  - Catheter-associated urinary tract infections
  - Ventilator-associated pneumonia
  - Surgical site infections
  - *Clostridium difficile* infection
  - Sinusitis
- **Non-infectious**
  - Thrombosis
  - Transfusion reaction
  - Hematoma
  - Postoperative fever
  - Myocardial infarction
  - Stroke
  - Central fever
  - Drug/alcohol withdrawal
  - Pancreatitis
  - Aspiration pneumonitis
  - Atelectasis

Crit Care Med 2009; 37(7 Suppl): S273-78.
Crit Care Med 2008;36(4): 1330-49.
Infect Dis Clin N Am 2009;23:471-84.

Drug Fever

- Fever that is temporally related to initiation of a drug
- Absence of other diseases or conditions that could be responsible for the fever
- Fever resolution after stopping the offending drug



Pharmacotherapy 2010;30(1):57-69.

Mechanisms of Drug Fever: Altered Thermoregulatory Mechanisms

- Increase heat production or limit heat dissipation
- Examples
  - Anticholinergic agents: decrease sweat gland secretion to prevent heat dissipation
  - Sympathomimetics (cocaine, MDMA, amphetamines): central and peripheral thermoregulation disturbances

Pharmacotherapy 2010;30(1):57-69.
AJHSP 2013;70:34-42

Mechanisms of Drug Fever: Drug Administration-Related Fever

- Fever occurs during or within hours of administration
  - Contamination of drug product
    - Pyrogens not removed during manufacturing
    - Rarely occurs today due to improved processes
  - Intrinsic pyrogenic activity of drug
    - Amphotericin B, bleomycin
    - Vaccines and allergenic extracts
  - Infusion-related phlebitis
    - Phenytoin, amiodarone, vasopressors, chemotherapeutic agents, dextrose, antibiotics

Pharmacotherapy 2010;30(1):57-69.
Am J Med Sci 1987;294(4):275-86.

Mechanisms of Drug Fever: Pharmacologic Action of the Drug

- Antineoplastic agents
  - Cancer cells damaged by drug release endogenous pyrogens that act on the hypothalamus
- Antimicrobial agents
  - Endotoxins released from killed or dying organisms act on the hypothalamus

Pharmacotherapy 2010;30(1):57-69.
Am J Med Sci 1987;294(4):275-86.

Mechanisms of Drug Fever: Hypersensitivity

- Most common mechanism of drug fever
- Humoral immune response
  - Drugs or metabolites act as antigens
  - Antibody-antigen complexes stimulate release of pyrogens, resulting in fever
- Cellular immune response
  - T-cell lymphocyte immune response results in endogenous pyrogen production to produce fever
  - Less common

Pharmacotherapy 2010;30(1):57-69.
Am J Med Sci 1987;294(4):275-86.

Mechanisms of Drug Fever: Hypersensitivity

- Cutaneous manifestations occur with drug fever in up to 30% of patients
- Fever may precede a more overt drug reaction or severe drug reaction
- Examples: antimicrobial agents (beta lactams and sulfonamides), phenytoin, carbamazepine, procainamide, quinidine

Pharmacotherapy 2010;30(1):57-69.

Drugs Reported to Cause Fever

- Antimicrobials
  - Acyclovir
  - Amphotericin B
  - Cephalosporins
  - Erythromycin
  - Nitrofurantoin
  - Penicillins
  - Rifampin
  - Trimethoprim-sulfamethoxazole
  - Vancomycin
- Cardiovascular
  - Diltiazem
  - Dobutamine
  - Furosemide
  - Heparin
  - Hydrochlorothiazide
  - Methyldopa
  - Procainamide
  - Quinidine
  - Quinine

Pharmacotherapy 2010;30(1):57-69.

Drugs Reported to Cause Fever

- Antineoplastics: 6-mercaptopurine, bleomycin, cisplatin, hydroxyurea, vincristine
- Immunosupressants: azathioprine, mycophenoalte mofetil, sirolimus
- NSAIDs: ibuprofen, naproxen
- Anticonvulsants: carbamazepine, phenytoin
- Others: allopurinol, cimetidine, metoclopramide, propylthiouracil, sulfasalazine, theophylline, thyroxine

Pharmacotherapy 2010;30(1):57-69.

Clinical Features

- Fever may occur at any time during a course of drug therapy
- Time from drug initiation to development of fever varies

Drug Class	Time to Fever
Antineoplastics	0.5 days
Antimicrobials	6 days
CNS agents	16 days
Cardiovascular agents	10 days

- Laboratory findings are highly variable and cannot be used for definitive diagnosis

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Am J Med Sci 1987;294(4):275-86.

Clinical Features

- Patterns of fever
  - Continuous fever
  - Remittent fever
  - Intermittent fever
  - Hectic fever
- Degree of pyrexia
  - Most common 102-104°F
- Patient may appear "inappropriately" well for degree of fever
- Relative bradycardia

Pharmacotherapy 2010;30(1):57-69.

My patient still has a fever…

- Two days later M.M. continues to have intermittent fevers up to 103.2°F. His blood cultures have been negative X 48 hours and a diagnostic work-up reveals no new source of infection. He also has no evidence of thromboembolic disease. His cefazolin was continued to treat the MSSA pnuemonia and his antibiotics were not broadened, since he had no signs or symptoms of infection except fever. Other than the fevers, he is extubated and doing well. His fentanyl and insulin drip have been discontinued. Given his negative diagnostic work-up so far, the team thinks M.M. could have drug fever. Which drug(s) are most likely to be the offending agent(s) and how would you consider altering the patients drug therapy?

My patient still has a fever…

- Aspirin
- Cefazolin
- Enoxaparin
- Famotidine
- Docusate
- Furosemide
- Simvastatin

Treatment

- Discontinue the suspected agent(s)
- Resolution of fever generally occurs in 48-72 hours
- Benefits of continued therapy may outweigh risk in some situations
  - Pretreat with prostaglandin inhibitors (i.e. acetaminophen or NSAIDs)
  - Closely monitor for additional signs of hypersensitivity
- Rechallenge

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My patient's fever has resolved

- M.M.'s famotidine and cefazolin were both discontinued. He no longer had an indication for SRMD prophylaxis so his famotidine could be stopped and he had completed his course of cefazolin for MSSA pneumonia, so cefazolin could also be stopped. The furosemide was continued since it was a home medication. The enoxaparin was continued for VTE prophylaxis. Two days later M.M.'s fevers have completely resolved.

Objectives

- Understand the pathophysiology, symptoms and treatment of
  - Serotonin Syndrome (SS)
  - Neuroleptic Malignant Syndrome (NMS)
  - Malignant Hyperthermia (MH)
- Be able to compare and contrast the presentation and treatment options for all three hyperthermia emergencies

Serotonin Syndrome

- Life-threatening syndrome
  - Increased serotonergic activity in the central nervous system
    - Overstimulation of serotonin 5-HT1A and 5-HT2A
  - Associated with
    - Therapeutic treatment
    - Overdosage
    - Drug interactions
  - Occurs in all age groups
    - Newborns to elderly patients
  - Onset
    - Hours to days of initiation or titration

Neurol Clin 30 (2012) 321–344
British Journal of Anaesthesia 105 (4): 417–20 (2010)
Emerg Med Clin N Am 25 (2007) 477–497
Neurol Clin 30 (2012) 305–320

Associated Medications

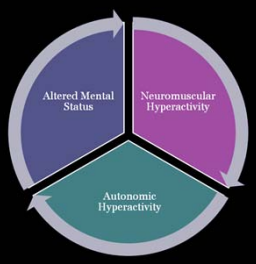
- Selective serotonin reuptake inhibitor (SSRI)
- Lithium
- Antidepressants
  - Amitriptyline
  - Amoxapine
  - Buspirone
  - Clomipramine
  - Desipramine
  - Doxepine
  - Imipramine
  - Nefazodone
  - Nortriptyline
  - Trazodone
  - Venlafaxine
- MAOIs
  - Phenelzine
  - Isocarboxazid
  - Selegiline
  - Tranylcypromine
- Anticonvulsants
  - Valproate
- Analgesics
  - Meperidine
  - Fentanyl
  - Tramadol
  - Pentazocine
  - Methadone

Associated Medications

- Antibiotics
  - Linezolid
  - Ritonavir
- Antimigraine
  - Sumatriptan
- Bariatric
  - Sibutramine
- Over-the-counter
  - Dextromethorphan
  - Chlorpheniramine
  - Brompheniramine
- Antiemetics
  - Ondansetron
  - Granisetron
  - Metoclopramide
- Drugs of Abuse
  - MDMA "Ecstasy"
  - LSD
  - Cocaine
- Dietary supplements
  - Tryptophan
  - St. John's wort
  - Ginseng

Mechanism of Action	Implicated Drugs
Impairs reuptake from synaptic cleft into presynaptic neuron	- SSRIs - TCAs - SNRIs - 5-HT3 anti-emetics
Increases release of serotonin	- Amphetamines and amphetamine derivatives - Cocaine, ecstasy - L-dopa - Sibutramine - Lithium - Buspirone
Increases serotonin formation	-L-tryptophan
Inhibits serotonin metabolism	- MAOIs - Linezolid
Direct serotonin agonist	- Buspirone - Triptans - Fentanyl

Symptoms



- ***Clonus***
- ***Hyperreflexia***
- Agitation
- Diaphoresis
- Tremor
- Anxiety
- Agitated
- Delirium
- Restlessness
- Disorientation

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Symptoms

- Severe disease
  - Core temperature >41.1ºC
  - Hypertension
  - Tachycardia
  - Muscle rigidity
  - Rhabdomyolysis
  - Metabolic acidosis
  - Renal failure
  - Seizures
  - Disseminated intravascular coagulation
  - Shock

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Serotonin Syndrome Treatment

- Stop offending medication
- Supportive care
  - No role for antipyretics
  - Hydration
  - Active cooling
  - Intubation
    - Paralytics may be necessary
  - Benzodiazepines
    - Lorazepam
      - 2 – 4 mg IV
    - Diazepam
      - 5 – 10 mg IV
  - Serotonin antagonists
    - Cyproheptadine

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Treatment Algorithm

Severity	Symptoms	Treatment
Mild	Hyperreflexia and tremor; no fever	-Removal of precipitating agent - Supportive care - BZDs for agitation
Moderate	Autonomic instability; potential for hyperthermia	-Above PLUS - Control all autonomic aspects - May benefit from 5-HT_2 antagonists (Cyproheptadine)
Severe	Temperature > 41.4 ºC	-Above PLUS - Immediate sedation, paralysis, and intubation

Cyproheptadine

- Mechanism of action
  - Histamine-1 receptor antagonist
  - Antagonizes 5-HT1A and 5-HT2A
  - Weak anticholinergic activity
- Dose
  - Initial:
    - 12 mg PO or via gastric tube
  - Followed by 2 mg every 2 hours
    - 4 – 8 mg every 6 hours
  - Max dose:
    - 30 mg or 32 mg/day

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Neuroleptic Malignant Syndrome (NMS)

- "Akinetic hypertonic syndrome"
- Serious idiosyncratic life-threatening emergency
  - Mortality rate
    - 10 – 20%
- Incidence
  - < 3%
- Gradually progresses
  - Severity increases within 48 to 72 hours
  - Duration
    - Up to 14 days

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Pathophysiology

- Exact mechanism is unknown
  - Dopamine receptors in different locations lead to unwanted effects
  - Direct muscle mitochondrial damage
  - Disrupted sympathetic nervous system activity
  - Genetic
- Antipsychotics
  - Antagonize dopamine receptors in:
    - Cerebral cortex
    - Basal ganglia
    - Limbic system
    - Hypothalamus
    - Chemoreceptor trigger zone

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Pathophysiology

- Antagonizing dopamine receptors in:
  - Hypothalamus
    - Hyperthermia and autonomic dysfunction
  - Mesolimbic
    - Positive symptoms
      Hallucinations and delusions
  - Nigrostriatal
    - Unwanted extrapyramidal movement disorders
  - Mesocortical brain region
    - Worsens the negative symptoms
      Withdrawal and poor motivation

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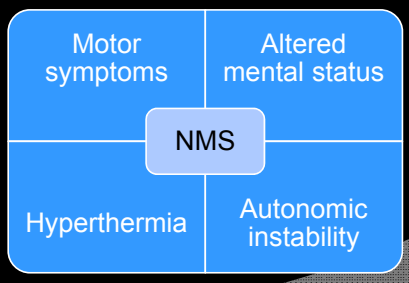
NMS Symptoms



NMS Symptoms

- ***Hyperthermia***
- ***Muscle rigidity***
- ***Autonomic dysfunction***
- ***Mental status changes***
- Akinesia
- Tremor
- Dystonias
- Dysphagia
- Dyspnea
- Diaphoresis
- Sialorrhea
- Incontinence
- Tachycardia
- Labile blood pressure
- Flushing
- Pallor
- Metabolic acidosis
- Liver function elevations
- Sodium imbalance
- Elevated white blood cell count
  - 10,000 – 40.0000
- Elevated serum creatine phosphokinase
- Coagulopathies
- Pulmonary embolism
- Renal failure.

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Associated Medications

WITHDRAWAL OF:

- Levodopa/carbidopa
- Amantadine
- Dopamine Agonists
  - Bromocriptine
  - Pergolide
  - Ropinirole
  - Pramipexole
  - Cabergoline
  - Apomorphine
- COMT Inhibitors
  - Tolcapone
  - Entacapone

INTRODUCTION OF:

- Neuroleptics
  - Phenothiazines: chlorpromazine, thioridazine, fluphenazine, perphenazine, trifluoperazine
  - Butyrophenones: haloperidol, droperidol
  - Thioxanthenes: chlorprothixene, thiotixene
- Atypical Antipsychotics
  - Clozapine
  - Olanzapine
  - Risperidone
  - Quetiapine
- Antiemetics
  - Metoclopramide
  - Droperidol
  - Prochlorperazine
  - Promethazine

Risk Factors

- Medication Risk factors
  - High doses
  - Rapid titration
  - Parenteral administration
  - Switching from one agent to another
- Onset
  - Occurs days to years after treatment initiation

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Additional Risk Factors

- Concomitant use of lithium
- Depot formulations
- Substance abuse
- Acute medical illness
  - Surgery
  - Trauma
- Dehydration
- Withdrawal of dopaminergic agents for Parkinson's disease
- Psychiatric conditions
- Organic brain abnormalities
- Genetics
- Catatonia

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NMS Treatment

- Stop offending medication
- Supportive care
  - No role for antipyretics
  - Hydration
    - Crystalloid
      - Account for losses from fever and diaphoresis
- Active cooling
  - Cooling blankets
  - Ice packs in axilla
  - Ice water gastric lavage
- Low dose heparin
  - Prevention of VTE

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Crit Care Clin 28 (2012) 587–600

NMS Treatment

- Benzodiazepines
  - Lorazepam
- Bromocriptine
- Amantadine
- Dantrolene
- Combination therapy
- Electroconvulsive therapy

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Bromocriptine

- Mechanism of action
  - Semisynthetic ergot alkaloid derivative and a dopamine receptor agonist
    - Restores lost dopaminergic tone
- Dose
  - 2.5 mg PO or gastric tube every 6 – 8 hours
    - Titrated to max of 40 – 45 mg/day
  - Continued for 10 days after resolution of symptoms

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Amantadine

- Mechanism of action
  - Blocking the reuptake of dopamine into presynaptic neurons
  - Increasing dopamine release from presynaptic fibers
  - Exhibits both dopaminergic and anticholinergic effects
- Dose
  - Initial:
    - 100 mg PO or gastric tube
  - Max dose:
    - 200 mg Q12 hours
- Warning
  - Abrupt discontinuation can precipitate NMS

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Crit Care Clin 28 (2012) 587–600

Dantrolene

- Mechanism of action
  - Direct-acting skeletal muscle relaxant
  - Prevents the increase in myoplasmic calcium ion concentration that activates the acute catabolic processes associated with malignant hyperthermia
- Dose
  - Initial:
    - 1 to 2.5 mg/kg IV
    - May repeat every 10 minutes up to max dose
  - Max dose:
    - 10 mg/kg/day
  - Continue for 7 days after
    - Usual duration about 2 weeks

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Restarting Neuroleptic Therapy

- Wait about 2 weeks
  - Longer if symptoms persist
- Use lower potency agents
- Start low and go slow
- Avoid dehydration
- Avoid precipitating agents
  - Lithium
- Monitor closely

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Malignant Hyperthermia

- Hypermetabolic crisis when an MH-susceptible individual is exposed to an inhalational anesthetic
  - Halothane, isoflurane, enflurane, sevoflurane, desfluranes
- Depolarizing muscle relaxant
  - Succinylcholine
- Incidence
  - 1:30,000 administered anesthetics worldwide
  - 50% of cases are in patients < 18
  - Males > females
  - Decreasing secondary to total intravenous anaesthesia (TIVA)
  - Occurs more often with 3rd exposure
  - Mortality rate has decreased with antidote
    - 70% to 17%
- Onset
  - Minutes to hours

Emerg Med Clin N Am 28 (2010) 595–609
British Journal of Anaesthesia 105 (4): 417–20 (2010)
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Neurol Clin 30 (2012) 321–344

Pathophysiology

- Malignant hyperthermia patients have a genetic predisposition
  - Mutations encoding for abnormal ryanodine receptors (RYR1) or dihydropyridine (DHP) receptors that trigger unregulated passage of calcium from the sarcoplasmic reticulum into the intracellular space
  - Accumulation of myoplasmic calcium causes sustained muscle contraction
    - Generates heat
    - Oxygen and adenosine triphosphate (ATP) stores are depleted
    - Anaerobic metabolism occurs
    - Leading to rhabdomyolysis

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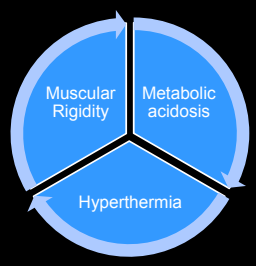
Malignant Hyperthermia Symptoms



Malignant Hyperthermia Symptoms

- Early signs
  - ***Elevated CO_2***
    - ***end-tidal CO2***
  - Mottling skin
  - Diaphoresis
  - Tachycardia
  - Ventricular bigemini or ectopic beats
  - Labile pressure
  - Rigidity
  - Mixed acidosis
- Late signs
  - Hyperkalemia
  - Hyperthermia associated with a rapid rise
  - Elevated blood creatine phosphokinase
  - Elevated myoglobin
  - Disseminated intravascular coagulation
  - Dark urine secondary to the myoglobinuria

Emerg Med Clin N Am 28 (2010) 595–609
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Treatment

- Stop trigger agents
  - Inhaled anesthetics or succinylcholine
- Supportive care
  - No role for antipyretics
  - Hydration
    - Crystalloid
      - Account for losses from fever and diaphoresis
  - Active cooling
- Increase oxygen
- Hyperventilate
- Change to TIVA
- Call for emergency
- Dantrolene
  - Hotline
    - United States: 1-800-644-9737

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Dantrolene

- Mechanism of action
  - Interfers with release of calcium ion from the sarcoplasmic reticulum in skeletal muscle cells
    - Binds to ryanodine receptors (RYR1)
  - Reduces the increase in myoplasmic calcium ion concentration that activates the acute catabolic processes associated with malignant hyperthermia

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Dantrolene

- Dose
  - Initial
    - 2.5 mg/kg loading dose
    - Additional doses of 1 mg/kg may be given
      - Rapid resolution should occur after initial doses
  - Maintenance dose
    - 1 mg/kg IV every 6 hours for 48 hours
    - Rebolus if symptoms reoccur
  - Max dose
    - 10 mg/kg
      - May be necessary in muscular males
    - Doses up to 30 mg/kg have been used
  - Administration
    - Initial dose should be given via rapid infusion
    - Additional doses may be given over one hour

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Dantrolene FYI…

- Mixing
  - Reconstitute 20 mg by adding 60 ml of sterile water for injection and shaking the vial until the solution is clear
  - May warm to speed reconstitution
  - Do not transfer to glass bottles
  - Use within 6 hours of preparation
- Stocking
  - 36 vials is recommended anywhere that performs surgeries with triggering agents
- Storage
  - In operating room
  - Malignant hyperthermia cart

http://www.mhaus.org/faqs/dantrolene

Manifestation	Serotonin Syndrome	NMS	Malignant Hyperthermia
Medication history	**Proserotonergic agent**	**Dopamine antagonist**	**Inhalational anesthesia**
Onset	**< 12 hours; may be days**	**1-3 days; up to 14 days**	**30 minutes-24 hours**
Vital signs	HTN, tachycardia, tachypnea, hyperthermia (>41.1)	HTN, tachycardia, tachypnea, hyperthermia (>41.1)	HTN, tachycardia, tachypnea, hyperthermia (as high as 46)
Pupils	**Mydraisis**	Normal	Normal
Skin	Diaphoresis	Pallor, diaphoresis	Mottled appearance, diaphoresis
Bowel sounds	**Hyperactive**	Normal to decreased	Decreased
Neuromuscular tone	**Increased; lower extremities**	**"Lead-pipe" rigidity**	**Rigor mortis-like rigidity**

Questions??