Malignant Hyperthermia

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Malignant Hyperthermia (MH)

- rare, potentially fatal pharmacogenetic disorder
- autosomal dominant inheritance
- develop a hypermetabolic crisis of skeletal muscle when exposed to halogenated inhalation agents or succinylcholine

Anesthesiology 2009; 110: 84-89

History of MH

- 1960 → 1st case report published in Lancet
- 1970 → correlations to Porcine Stress Syndrome
- 1970s → muscle biopsy testing begins
- 1979 → FDA approves dantrolene for use
- 1985 → dantrolene shown to reverse intracellular hypercalcemia in skeletal muscle
- 2003 → genetic tests identified for diagnostic use

Incidence of MH

- 500 to 800 suspected cases each year
- rare event → many cases are not found to be MH
- overall incidence in anesthesia: 1:3000 to 1:50,000
  - reported incidence has wide range in literature
- adult incidence: 1:50,000 anesthetics (1:100,00)
- children: 1:5000 to 1:10,000 anesthetics (1:30,000)
  - peak mean age: 18.3 years of age
  - children under the age of 15 → account for 52.1% of all cases
  - earliest age report → 6 months old

Anesthesiology. 2009;110: 89-94 Anesthesiology. 2014; 120: 1333-8
OOO.2011;112:e1-e7 Anesthesiologynews.com. Oct 2014

Incidence of MH

- males > females → ratio of 2:1
- inpatient surgery rate → 1:100,000
- ambulatory surgery rate
  - low incidence 0.31 per 100,000 cases
  - ASA Refresher Course 2011: at least 5 cases in ambulatory centers
- 30% patients won't react until the third exposure to triggering agents

Mortality from MH

- 70 to 80% mortality during 1960s to 1980s
- 11.7% mortality rate reported in 2009
- < 5% rate in 2013 (as low as 1.4%)
  - due to widespread use of dantrolene in MH reactions
  - due to early perioperative recognition of rising end tidal CO_2 by capnography
  - halothane is not being used
  - decreased use of succinylcholine with inhalation agents
- rate increase to 9.5% in 2014

Anesth Analg. 2014;118:388-396
Anesth Analg. 2013;116:118
Anesth Analg. 2014;119:1359

Muscle Contractions

- Ca^{++} mediates skeletal muscle contractions
  - in resting state, Ca^{++} is stored in the sarcoplasmic reticulum -- not the muscle cytoplasm
- Acetylcholine binds to muscle receptors → get depolarization → Ca^{++} released from SR → enters cytoplasm through RYR1 (ryanodine) receptor channels

Muscle Contraction

- Ca^{++} binds to troponin
  - allows actin to bind to myosin to shorten the muscle fibers
  - muscle now contracts
- ATP in cytoplasm stops the actin-myosin reaction
  - also pumps excess Ca^{++} back to sarcoplasmic reticulum
- ATP reaction is exothermic

Pathophysiology of MH

- RYR1 receptor channel remains open
  - also have a defect in the voltage regulator for the channel to help keep the RYR1 open
- Calcium continues to flow into the intracellular cytoplasm
  - develop hypercalcemia in the skeletal muscle
- Results in hypermetabolic reaction in muscle

Pathophysiology of MH

- RYR1 defect is primary mechanism in MH
- Secondary mechanism in MH
  - non selective cation channels in sarcoplasmic reticulum
    - they release Ca^{++} into the cytoplasm during an MH reaction
    - they also release Ca^{++} into the cytoplasm at rest as well
    - result is that MHS patients have higher than normal cytoplasmic Ca^{++} levels

MHS is Malignant Hyperthermia Susceptible

Hypermetabolic State

- aerobic metabolism drives the events at first
  - oxygen consumption V_{O2} is increased 3X normal
  - ATP stores are exhausted in attempt to stop contractions & pump Ca back into the SR
- ATP depletion causes exothermic reaction
  - heat production = hyperthermia of MH
- Anaerobic metabolism now takes over
  - develop metabolic acidosis

Anaerobic Metabolism

- acidosis develops → cells die → release K^+ into the circulation
  - hyperkalemia
    - monitor shows tall, peaked T waves
  - lactic acid levels are 15 to 20 times normal levels → metabolic acidosis
- muscle cell necrosis
  - myoglobin is released into the circulation
  - debris enters the circulation and ↑ blood viscosity
  - ↑ capillary obstruction
  - develop renal damage & coagulopathy

Death from MH

- hypoxia secondary to acidosis
- compromised blood flow to organs
  - especially kidneys = renal failure
- dysrhythmias secondary to hyperkalemia
- DIC develops especially if *temperature is greater than 41.5° C*
  - rarely do patients survive if DIC develops
  - 50 fold ↑ cardiac arrest 89 fold ↑ death

Anesthesiology. 2009;110:89

Malignant Hyperthermia MH

- hypermetabolic response to potent, volatile inhalation agents
  - halothane (no longer in US) > isoflurane
  - sevoflurane > desflurane
    - less potent than halothane & isoflurane
    - desflurane is least potent MH trigger
- depolarizing muscle relaxant agents
  - succinylcholine
  - succ + volatile agents ---- see more intense reaction
- rarely seen: non anesthesia cases of heat & vigorous exercise

Malignant Hyperthermia MH

- MH can occur on 1st exposure to a trigger
- 30% of cases take at least 3 exposures to trigger agents before MH is seen
  - reports exist where it took up to 10 anesthetic exposures before MH occurred
- Rare to see succinylcholine as a solo triggering agent: usually need volatile gas in addition
  - MH registry 6 out of 500+ cases only had succinylcholine as the trigger
    - all cases reported it took a dose of succ > 0.5 mg/kg
    - what is dose for laryngospasm?

Personal communication MHAUS - Brandom

2010 MH Case Reports

284 Cases of Malignant Hyperthermia (1987 to 2006)

Agent	% of MH cases
Enflurane	2.8%
Desflurane	12.1%
Halothane	15.6%
Sevoflurane	20.6%
Isoflurane	57.8%

Agents Used	% of MH Cases	Total Number
Volatile Gas Alone	45.1%	128 of 284 cases
Gas + Succinylcholine	53.9%	153 of 284 cases
Succinylcholine Alone	0.7%	2 of 284 cases

Anesth Analg. 2010; 110: 498-507

2014 MHAUS Registry Review

- 712 cases reported to MHAUS Registry 1987-2010
- 477 cases met criteria
  - 58.5% possible MH 41.5% fulminant MH
- Results
  - inhalation agent + succinylcholine 53.9% cases
  - inhalation agents alone 47.1% cases
  - succinylcholine alone 2.9% cases
  - no trigger agent used 7 cases out of 477

Anesth Analg. 2014; 118(3):388-396

394 Single Agent Cases

- Volatile Agent without succinylcholine
  - halothane had fastest onset → statistical difference among all 4 agents
- Volatile Agent + succinylcholine
  - onset was shorter in all agents used

Anesth Analg 2014

MH Onset Time in Presence or Absence of Succinylcholine				
MH Onset Time (minutes)				
No Succinylcholine			*Succinylcholine*	
Agent	*Number Cases*	*Median minutes*	*Number Cases*	*Median minutes*
Halothane	*16*	*15.5*	*63*	*10*
Sevoflurane	*56*	*45*	*37*	*30*
Desflurane	*22*	*113.5*	*30*	*50*
Isoflurane	*67*	*135*	*103*	*65*

1 Unique First Sign of MH

- Typical early signs of MH
  - ↑ end tidal CO_2 , muscle rigidity, sinus tachycardia, masseter muscle spasm (MMS)
- Can have a single unique 1st sign as well
  - 322 cases of 477 had a single 1st sign
    - hypercarbia 30.7% (illustrates the need for capnography)
    - masseter muscle spasm 24.8%
    - sinus tachycardia 21.1%

Masseter Muscle Spasm (MMS) is also known as Masseter Muscle Rigidity (MMR)

MH Onset with Succinylcholine but no Inhaled Agents

- 14 cases where succinylcholine was used but no inhaled agent (14 out of 477)
  - 11 of 14 (78.57%) had possible MH
  - 3 of 14 (21.42 % had fulminant MH
  - dose was not defined → assume it was for intubation
- most frequent initial signs
  - masseter muscle spasm & sinus tachycardia (50%)
  - hypercarbia (35.7%)
  - elevated temperature (28.6%)

Anesth Analg. 2014; 118:388

MH Onset with Succinylcholine

- Succinylcholine is used in only 5 to 10% of all general anesthetics
- as solo agent → low risk of MH reaction
  - Canadian review: 20 out of 129 MH cases (~ 16% of cases)
    - higher rate than other case reports
    - dose range of 0.5 to 2.5 mg/kg
- Succinylcholine + volatile gas: > 50% of reported MH cases

Anesth Analg. 2013;116:118

Summary from 2014 Report

- Combination of inhaled anesthetics & succinylcholine has the fastest onset of MH
- MH onset time is very rapid when see MMS after use of succinylcholine
- Halothane has fastest onset compared to other gases
- Sevoflurane has faster onset than desflurane and isoflurane
- Since 1998 MH appears more so in 2nd or 3rd hour of anesthesia

Anesth Analg. 2014;118(2): 388-96

Delayed Onset of MH

- Sevoflurane anesthesia
  - median onset → 60 minutes
  - range → 10 to 210 minutes
- Halothane anesthesia
  - median onset → 20 minutes
  - range → 5 to 45 minutes
- Use of non-depolarizing NMB agents
  - delay the onset of MH and result in ↓ in CK levels

AANA Journal. 2013;81(6): 441-445

Br J Anesthesia. 2011;107:48-56

Clinical Manifestations of MH

- Early descriptions of MH reactions in literature
  - all patients have generalized muscle rigidity
  - high fevers & acidosis
  - high mortality rate
- Current descriptions in literature
  - muscle rigidity may or may not be present
  - temperature increase is a "late finding"
  - *CO_2 increase is an early sign*
  - occur at any time during anesthetic even post operatively
  - recrudescence may occur despite treatment with dantrolene

Classic Malignant Hyperthermia

- the *sine qua non*, ↑ in end tidal CO_2
  - if you increase the minute ventilations, you will still see an ↑ in end tidal CO_2 → it just may be delayed
  - intubated patients end tidal levels of ≥ 55 mm despite aggressive ventilation
  - *has been described as the earliest & most sensitive sign of MH*
    - *reinforces the need for capnography*
- tachycardia & tachypnea
  - overbreathing the ventilator is frequently seen
  - if open airway technique, you will see tachypnea

Classic Malignant Hyperthermia

- muscle rigidity in all of the extremities
  - may not always be present
- hypertension
- ventricular dysrhythmias secondary to hyperkalemia
- increase in temperature 1 to 2° C Q5mins
  - 2.9 fold ↑ in complications for every 2° C ↑ in temperature
  - temperatures > 41.5° lead to coagulopathies including DIC
- increase temperature in CO_2 absorbent canister
  - look for the "blue – purple" canister
- peripheral skin mottling, sweating, & cyanosis

Classic Malignant Hyperthermia

- hyperkalemia & hypercalcemia
- cola colored urine = myoglobinuria
- acidosis as measured by blood gases
- increase in CK
  - ≥ 20,000 U in 1st 12 to 24 hours
  - not always a consistent finding → if present, most likely MH reaction
- DIC
  - PT, PTT, d-dimer
  - ↑ in risk of death (89 fold increase)
  - ↑ in risk of cardiac arrest (50 fold increase)

Anesthesiology. 2009; 110: 89-94

Classic Malignant Hyperthermia

- Patients with increased muscle mass
  - ↑ in risk of death (14 fold increase)
  - ↑ in risk of cardiac arrest (19 fold increase)
- Longer it takes $EtCO_2$ to peak
  - greater the risk of death or cardiac arrest

Exceptions

- succinylcholine + inhalation agents
  - 1st sign is more likely to be muscle rigidity especially masseter muscle rigidity (MMR) (MMS)
  - ↑ in $EtCO_2$ will follow along with hyperthermia and tachycardia
- hyperthermia
  - typically not the first sign
  - "late sign" is relative term → it just follows the others but not by that much

MH in Children

- reported incidence depends upon study
  - Anest Analg. 2014: incidence of MH is 17%
  - # 1 (0 - 24 months old) #2 (25 mo- 12 yr.) #3 (13- 18 yr.)
- most common findings in all 3 groups
  - tachycardia (73.1%)
  - hypercarbia (68.6%)
  - rapid temperature elevation (48.5%)
  - group 3 → more likely to develop these findings
- Group 3
  - took longer to get to maximum end tidal levels
  - had higher K^+ levels, more rhabdomyolysis, higher CK levels

MH in Children

- Group 1
  - higher levels of metabolic acidosis
- Recrudescence rate 14.4% vs 20% in adults

Clinical	Age 0 to 24 months	Age 25 months to 12 yr	Age 13 to 18
Sinus tach	74.3%	67.5%	86.4%
Hypercarbia	77.1%	58.3%	89.4%
Rapid ↑ temp	37.1%	31.3%	66.7%
Max End tidal	75.9 mm	62.8 mm	75.2 mm
Time to Max end tidal CO2	640.8 min	682.1 min	861.7 min
pH	7.16	7.23	7.2

Anest Analg. 2014; 118: 369 - 74

Post Operative MH

- MH can occur any time perioperatively
- Post op MH
  - 1.9% of all cases in MH – N. America registry
  - maximum latency period is unknown
  - onset usually 0 to 40 mins post operative
  - *hyperthermia not a usual presenting sign*
  - most of these cases are atypical presentations
  - may only see rhabdomyolysis & cola-colored urine
    - *myoglobinuria* → *urine dip stick in office*
- Refer for MH testing to confirm
  - muscle biopsy and/or genetic testing

Anesthesiology 2008; 109 (5)

Recrudescence of MH

- recurrence of successfully treated MH crisis ≥ 2 hrs after initial reaction
- incidence in adults is 20% (63 out of 308 cases)
  - 50% cases within 9hrs
  - 80% cases within 16 hrs
- greater the intensity of the initial reaction
  - the more likely to see episode of recrudescence
- no correlation to dose of dantrolene used in initial reaction & risk of a recurrent reaction

Recrudescence of MH

- ↑ in muscle mass will double risk of recrudescence
- the longer it takes for the initial reaction to occur
  - get an ↑ in risk of recrudescence
  - greater exposure of muscle to trigger agents is a risk factor
- hyperthermia may be the only sign seen
- desflurane is weakest trigger → no cases reported

Anesthesiology 2007; 106(5): 902-906 Anesthesiology. 2007; 106: 893-894

Trigger Agents

- halothane (no longer manufactured in US)
- isoflurane
- sevoflurane & desflurane
  - desflurane < sevoflurane < isoflurane < halothane as trigger
- succinylcholine
- older agents: ether, enflurane, & methoxyflurane
- question? Is it the agent itself or the dose of the agent that causes MH?

Non Trigger Agents

- antibiotics & antihistamines
- local anesthetics & nitrous oxide
- barbiturates, propofol, & etomidate
- benzodiazepines, opioids, & ketamine
- droperidol & non depolarizing neuromuscular paralyzing agents

Temperature Monitoring

- MHAUS → monitor temperature for all GA > 30 mins
- Core temperature is preferred method
  - tympanic membrane → soft probe touching membrane → difficult to insert
  - esophageal probe in an esophageal stethoscope
  - nasopharynx → less accurate in open airway breathing through nose
  - urinary bladder & rectum are considered intermediate sites
    - temperature changes here lag behind changes in core temperature
  - core temperatures are more accurate than peripheral temperatures

Anesthesiology. 2008; 109:318-338

Peripheral Temperature Monitors

- axilla → probe must be over the axillary artery with the arm covering it
  - underestimates the core temperature
- forehead liquid crystal skin strips
  - forehead skin subcutaneous insulation is minimal compared to other sites in body
  - sweating & shivering → little effect on readings
  - clinically accurate for anesthetic monitoring → remember the core temperature is 2^{o} higher
  - MHAUS → not acceptable for MH temperature monitoring
  - our setting is an office → we have certain limitations
- infrared tympanic → poor fit in ear canal
  - clinically inaccurate

Importance of Temperature Monitoring

- 30% mortality rate if temperature not monitored
- 21% mortality rate if relied on skin monitors
- 2% mortality rate if used core temperatures
- skin temperature instead of core temperature
  - 50% increase in mortality
- no temperature vs core temperature
  - 2 fold increase in mortality
- elevated temperature better identifies risk of death
  - better than K^{+} , pH, arterial CO_2 , or end tidal CO_2

Anesth Analg. 2014;119:1359-66

Testing for Malignant Hyperthermia

Caffeine Halothane Contracture Test CHCT

- MHAUS → CHCT is gold standard at present
- muscle biopsy under GA
  - can not use local anesthesia - may alter test results
- sensitivity = 97% (false negatives rare)
- specificity = 78% (false positives rare)
- need to wait for 3 to 6 months after suspect MH event or significant rhabdomyolysis to test

MHAUS Web Site

Malignant Hyperthermia (MH)

- inherited as an autosomal dominant
- 2 genes linked to MHS
  - MHS 1 is the RYR1 gene
    - genetic mutations account for 50% to 70% cases of MHS patients
  - MHS 5 is the CACNA1S gene
    - mutations account for ~ 1% of MHS patients
- genetic testing identifies only 25 to 30% of patients with confirmed MHS

Anesthesiology Newsletter. Oct 2014 Anesth Analg. 2014; 118: 397-406 & 375-380

RYR1 Gene

- located on chromosome 19 (19q13.1-13.2)
- contains 106 exons of mRNA amino acid sequences
  - all capable of multiple mutations
    - at present 397 variations
    - **as of 2014 → 31 are causative**
    - in 2014 another 2 recommended (R2355W & V2354M)
- some patients may have ≥ 1 mutation in RYR1
  - 2 or more mutations → compound heterozygous
  - greater incidence of MH 1:2000 to 1: 8500

Anesth Analg. 2014; 118: 375-380
Anesth Analg. 2014; 118: 397-406
Anesthesiology. 2008; 108: 208-215

Tiered Genetic Testing

- Tier 1 testing → blood test
  - look at 3 "hot zones" on RYR1 known to have causative mutations
  - 17 exons examined
  - 23% sensitivity
- Tier 2 testing → blood test
  - looks at entire RYR1 gene
  - 70 to 80% sensitivity
  - very expensive compared to Tier 1
- Discordance Rate of 10%
  - muscle biopsy positive but negative genetics
  - unexplained at present

Genetic Testing

- not all MHS patients have known causative mutations
  - *genetic testing can not replace muscle biopsy at present*
- however, once a causative mutation is found in a family
  - family members can get the genetic test first
  - if the causative mutation is found in their test, they are MHS positive
    - there is no need for them to get a muscle biopsy

Curr Opinion Anaesth. 2009; 22: 744

Genetic Tests – Pros & Cons

- Pros
  - less expensive than CHCT
  - far less invasive than CHCT
  - no need to travel
- Cons
  - discordance – CHCT results differ from genetic results
  - due to heterogeneity of MH, absence of causative mutation does not rule out MHS
    - still need a muscle biopsy
  - still expensive: $800 to $4000 for a partial to full gene scan

MHAUS web site

Management of MH Crisis in the Office

Office Plan for MH Reaction

- need protocol in place
  - assigned doctor and staff duties
  - transfer protocol to a specific hospital where MH can be treated
    - dantrolene on site
    - critical care on site
    - anesthesiologist on site
    - MHAUS hotline 1-800-644-9737
  - transfer protocol with local EMS
    - 911 call → declare MH emergency with transfer to specific institution
    - EMS alerts hospital → have anesthesiologist in ER
    - do not delay transfer → you can give dantrolene in transit

Anesthesia Machine Preparation

- dedicated vapor free workstation
  - expensive & impractical
- intensive care ventilator
  - unit never exposed to volatile anesthetic agents
- unit that was treated with a "machine flush"
  - drain – disable – remove vaporizer from unit
  - flush with fresh gas 10 L/min for **> 90 minutes**
    - **each manufacturer has specific guidelines**
  - change anesthesia circuit, breathing bag, & CO_2 absorbent
  - keep gas flows at **> 10 L/min** to prevent rebound phenomenon
    - residual volatile gas diffuses out of plastic parts in unit
- charcoal filters

Anesth Analg. 2014; 119:67-75

Vapor-Clean Charcoal Filters

- disposable filters
  - sterilization renders them useless
- can be used in an acute MH reaction
- can be used to prevent an MH reaction
- approved for isoflurane, sevoflurane, & desflurane
  - removes at least 99% of anesthetic vapors
- effective for 12 hours if not exposed to volatile agents
- will not capture or scavenge nitrous oxide

www.dynasthetics.com

Vapor-Clean Filters

- turn off vaporizer
  - tape it shut so it can not be turned back on accidentally
- flush unit for 90 seconds at 10 L/min of fresh gas
- place filters on inspired and expired unit ports
- replace bag & circuit
- maintain fresh gas at **> 10 L/min**
- reduces volatile agent to **< 5 ppm in < 2 minutes for 90 minutes**
- no need to replace anesthesia machine

Vapor-Clean

- 8 filters (4 pair) retail $599.00

Office Equipment & Supplies

- monitors
  - capnograph
  - ECG, SpO_2 , HR, BP, & temperature
- refrigerated IV solutions: NSS
  - no LR because of calcium & potassium in solution
- ice for axilla, groin, legs
  - reusable ice packs less mess
  - do not cool below 37.5 to 38° C → develop hypothermia
- 60 ml syringes (5) to mix & deliver dantrolene
- consider NG tube for cold lavage?

Medications

- dantrolene
  - 36 vials of 20 mg dantrolene or 3 vials of Ryanodex
- bacteriostatic free sterile water to dilute dantrolene
  - 60 mls needed to dilute → stock 100 ml vials
- ventricular dysrhythmias
  - 2% lidocaine pre filled syringes
  - amiodarone 300 mg vial
- sodium bicarbonate 8.4% 50 ml prefilled syringe
  - management of acidosis should be dictated by blood gases
- other advanced emergency medications

Dantrolene

- standard of care for MH reaction
  - only available treatment to reverse an MH episode
- acts within muscle cell to prevent Ca^{++} release from the sarcoplasmic reticulum (SR)
- it is a skeletal muscle relaxant
  - affects the contractile response of muscle
- MHAUS → must be available within 10 minutes of the decision to treat
  - previous 5 minute time impractical
  - 1.5 times ↑ in complications for each 30 min delay in giving drug

Dantrolene

- **initial dose 2.5 mg/kg IV bolus**
  - **given based upon total body weight → not lean body weight**
  - **some sources say limit is 10 mg/kg → others disagree**
  - **additional doses based upon continuation of symptoms**
    - **continued ↑ in temperature, $EtCO_2$, acidosis, & tachycardia**
  - **therapeutic levels for 4 to 6 hours**
- **why is there mannitol in dantrolene??**
  - **diuresis of kidneys**
  - **dantrolene is insoluble**
    - **mannitol allows dantrolene to go into solution**

Personal communication: Dr. Herlich

Dantrolene

- If MH reaction returns → recrudescence
  - additional dose of dantrolene up to cumulative dose of 10 mg/kg
- all cases of MH → ICU admission for 36 hours
  - dantrolene 1 mg/kg IV Q 4 to 6 hours for next 24 hours
  - monitor coagulation
  - myoglobinuria monitor with heme test strip
    - if positive → maintain urine output at 2 ml/kg/hr
  - monitor K^+ and CK levels Q 8 h

Dantrolene Side Effects

- most common is muscle weakness
  - occurs in 25% of cases where dantrolene is used
  - dantrolene + non depolarizing NMB agents compound the weakness
    - make sure muscle strength has returned prior to extubation
- sterile phlebitis
  - ~ 11% of cases
  - treat with warm soaks and elevation of extremity
- in clinical doses for MH
  - rare to see myocardial contractility defects
- nausea & vomiting

Dantrolene Side Effect

- dantrolene & calcium channel blockers
  - dangerous combination
  - 2 common IV calcium channel blockers for emergency use
    - verapamil
    - diltiazem
- side effects of concern from the combination
  - hyperkalemia
  - myocardial depression
- no apparent, significant negative interactions with other medication

Dantrolene (Dantrium)

Newer Brand Name Version → Reconstitute in 20 seconds

Dantrolene

- Generic version will take several minutes to reconstitute → delays treatment onset

Dantrolene (Revonto)

- generic version by US World Meds
  - www.usworldmeds.com
- reconstitutes in ≤ 20 secs with sterile water
- 36 vials is full dose
- can get it in packs of 6 vials

Revonto

- Reconstitute 20 mg vial with 60 ml sterile water
  - not bacteriostatic water
  - shake for 20 seconds until see clear liquid
  - use within 6 hours
- Each vial contains
  - 20 mg dantrolene
  - 3000 mg mannitol
  - sodium hydroxide to keep pH at 9.5 when mixed with water
  - need to supply 60 ml bacteriostatic free sterile water
- Shelf life → 36 months
  - store at 68-77° F and avoid light exposure
- Cost → $376 for 6 vials (Jan 2015)

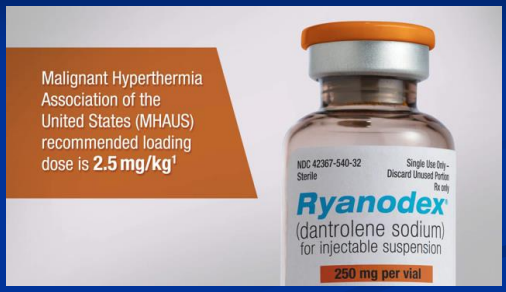
Dantrolene (Ryanodex)

- FDA approved in 2014
- Each vial has 250 mgs dantrolene
  - equivalent of 12.5 vials of other dantrolene preparations
  - total initial dose of dantrolene for a 100 kg patient
- Mix with 5 ml sterile water
  - reconstitutes in **≤ 1minute → usually in 10 seconds**
  - concentration is **50 mg/ml**
  - opaque, bright orange color when mixed
- Must use it within 6 hours
- Shelf life of 24 months

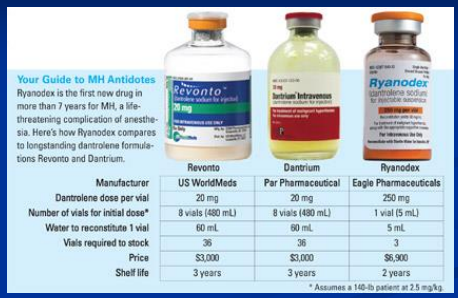
Ryanodex

- Vial only has 125 mg of mannitol
  - subtherapeutic diuretic dose for protecting kidneys
  - other dantrolene products have 3000 mg of mannitol per vial
  - may need to address diuresis with other agents
- Use 99% less water with this product
  - some benefits → some disadvantages
  - sterile water without bacteriostatics
- MHAUS recommends minimum of 720 mg
  - 3 vials of Ryanodex
  - many MH reactions require median dose of 5.9 mg/kg which is more than the 3 vials
- Cost → $2300 per vial

Ryanodex



Comparisons



Costs: $3000.00 $3000.00 $6900.00

Management in Office

- activate 911 to initiate transfer
- turn off inhalation gases & stop succinylcholine
- switch to nontriggering TIVA anesthesia
- 100% O_2 flush for 90 seconds at 10 L/min
  - do not replace anesthesia machine → place Vapor-Clean filters → replace anesthesia circuit and breathing bag → keep gas flow > 10 L/min
- dantrolene 2.5 mg/kg IV bolus
  - many cases may respond to initial dose
  - EMS should be there by time dantrolene mixed and administered
- give chilled IV NSS → apply external ice packs

Office MH Reactions

- Primary goal in office
  - make the diagnosis
  - initiate transfer
  - get dantrolene into solution
- Takes 30 minutes on average to get to this point
  - EMS should be there by now
  - Do not delay transfer
  - Secondary management is very limited

Secondary Management

- ventricular dysrhythmias
  - most likely due to hyperkalemia
    - do you stock $CaCl_2$, Ca-gluconate, or regular insulin- dextrose in your office
    - tall, peaked T waves or very wide QRS complexes may be hyperkalemia but you don't know
  - amiodarone: 150 mg for V-tach 300 mg V-fib
  - 2% prefilled lidocaine 100 mg as alternative
- EMS still not there after dantrolene bolus given
  - looking at 20 to 30 minutes by now
  - metabolic acidosis: sodium bicarbonate
    - consider 1 to 2 mEq/kg IV in office (unlikely)

Patient Transfer

- do not advocate a "grab & go" from an office
  - prepare dantrolene in office & support patient until EMS arrives
- can not get laboratory values in office
  - primary care is limited to
    - stopping the trigger
    - 100% O_2
    - dantrolene for bolus
    - initial dysrhythmia management
    - ice packs for cooling
  - secondary care is working blindly without data & should not delay any transfer to a facility where comprehensive care can be delivered

Anesth Analg. 2012;114:94-100

Indicators of Stability

- $EtCO_2$ is declining or returns to normal
- Tachycardia is improving
- No ominous dysrhythmias
- Temperature is declining
- Generalized muscle rigidity is resolving
- IV dantrolene administration

Other Management Issues & Special Circumstances

Hyperkalemia

- K^+ levels > 5.9 or less if there are consistent ECG changes
  - tall peaked T waves or very wide QRS
- insulin + glucose
  - insulin drives K^+ back into cells → glucose prevents hypoglycemia
  - Adults: 10 U regular insulin + 50 mls of 50% dextrose IV
  - Children: 0.1 U/kg regular insulin + 1.0 ml/kg 50% dextrose
    - may need to dilute to 25% dextrose to decrease irritation to veins
  - add albuterol by MDI or nebulizer to further drive K^+ into cell

Hyperkalemia

- MH presents with hypercalcemia
  - no contraindication to using Ca to treat hyperkalemia
  - Ca is used to stabilize myocardial cells to prevent dysrhythmias
- $CaCl_2$ → 10 mg/kg IV (max dose 2000 mg)
  - more effective than Ca-gluconate
  - central line preferred route
- Ca-gluconate → 30 mg/kg IV (max dose 3000 mg)
  - less irritation to veins
  - can avoid central lines & use peripheral line
- Lasix 0.5 to 1.0 mg/kg IV (max 20 mg) 1 dose

Myoglobinuria

- assume myoglobinuria is present if
  - labs show an ↑ in Creatine kinase (CK) and K^+
- need to alkalinize urine to prevent renal tubular necrosis
  - sodium bicarbonate 1 mEq/kg/hr
- maintain urine output at > 1ml/kg/hr
  - mannitol in dantrolene will cause diuresis

Masseter Muscle Rigidity MMR

- masseter muscle spasm after inject succinylcholine
- incidence 1: 12,000 GA
- more common in children & adolescents
  - 1: 100 to 1:5000 general anesthetics using volatile gas + succinylcholine
- **it is associated with MHS**
  - **occurs in ~ 50% of MHS patients**
- most cases induced by volatile agent + succinylcholine
  - TIVA cases + succinylcholine are less common
- *"tight jaw is not due to light anesthesia"*

Masseter muscle rigidity (MMR) is same as Masseter Muscle Spasm (MMS)

Masseter Muscle Rigidity MMR

- additional doses of succinylcholine or non depolarizing NMB agents
  - will not reverse the spasm
- 30% of MMR cases
  - immediate onset of MH crisis
- majority of cases of MH
  - occur in ~ 20 minutes post trigger exposure

Advice for Inpatient MMR

- elective surgery → stop the surgery & monitor for MH reaction over several hours
- emergency surgery → start MH protocol
  - stop triggering agents & switch to TIVA instead of volatile gas
  - flush volatile gas out for 90 secs at 10 L/min & place Vapor-Clean
    - maintain 100% O_2 at > 10 L/min
  - only proceed with surgery if dantrolene is on site
  - capnography is mandatory + monitor for other signs of MH
    - if MH reaction starts → stop surgery and treat MH
    - hospital case: keep for 12 to 24 hours
  - look for myoglobin in urine
  - follow CK levels → levels > 20,000 units MH likely

Office MMR

- if seen in an office (especially child or teenager)
  - early transfer is far better than waiting for a fulminant reaction
  - succinylcholine was given → tight jaw is not due to light anesthesia
- start your office protocol
  - stop triggering agents → let the patient wake up
  - initiate transfer
  - 100% O_2 & prepare machine if volatile gases were used
  - get dantrolene & monitor for signs of MH
- be smart & transfer out

Myodystrophies & Anesthesia

- Duchenne Muscular Dystrophy
- Becker Dystrophy
- These patients develop cardiac arrest after succinylcholine or volatile anesthetic agents
  - due to release of potassium from muscle cells along with release of myoglobin
- Resembles a MH crisis
  - not felt to be true MH

Succinylcholine Induced Hyperkalemic Rhabdomyolysis & Cardiac Arrest

- Apparently healthy children with acute onset hyperkalemia & rhabdomyolysis within minutes of succinylcholine use
- *ventricular dysrhythmias & sudden cardiac arrest within mins of succinylcholine use*
  - peaked T waves seen on EKG
- males, usually age 8 or younger
  - on autopsy, muscular myopathy usually Duchenne's

Succinylcholine Induced Hyperkalemic Rhabdomyolysis & Cardiac Arrest

- if you don't suspect inadequate ventilation & hypoxia or anesthetic overdose as the cause
  - immediately start treatment for hyperkalemia
  - calcium, glucose + insulin, bicarb, & hyperventilate
- resuscitation attempts are usually unsuccessful
- FDA placed black box warning
  - avoid succinylcholine in children and young adults for elective surgery
- Avoid succinylcholine
  - major burns, stroke, and spinal cord injuries

MH Associated Disease

- Central Core Disease CCD
  - many case reports of MH in CCD patients
  - gene mutations on RYR1 gene
- Myotonias
- King-Denborough Syndrome

Awake Malignant Hyperthermia

- Exertional heat related illness
  - triggers: high environmental temperatures, high humidity, & strenuous physical activity
  - symptoms
    - confusion, dizziness, fatigue, HA, & syncope
    - profuse sweating, hyperthermia, & tachycardia
    - dark colored urine
      - most likely dehydration so urine is concentrated
      - or myoglobin in urine from rhabdomyolysis
  - may progress to heat stroke if left untreated

Awake Malignant Hyperthermia

- Heat stroke
  - usually seen in extremes of age: < 4 or > 65
  - men > women
  - often a progression of exertional heat exhaustion
  - symptoms
    - confusion, agitation, slurred speech, delirium, seizures, & coma
    - hyperthermia > 104 F or 40 C
    - skin
      - vasodilated
      - moist in exertion dry in non exertional heat stroke
    - tachycardia, N/V, & tachypnea
    - hyperkalemia, rhabdomyolysis, & multiple organ failure
  - untreated mortality 21%

Awake Malignant Hyperthermia

- Management of Heat Exhaustion & Stroke
  - get out of sun into air conditioned room
  - hydrate PO and IV & active cooling measures
- Heat Stroke
  - no association to MH at present
- Exertional Heat Exhaustion
  - 1% of MHS patients report history of heat related problems
  - case reports of positive RYR1 MH mutation patients having
    - "awake MH" reactions

Pediatric Anesthesia.2013;23:842

MHAUS Guidelines

- Non – anesthetized MHS patient suffering sudden collapse, muscle rigidity, and hyperthermia
  - treat with dantrolene & active cooling
  - no succinylcholine if need to intubate
- MHS patient or relatives with no adverse effects from heat & excercise
  - no need to limit activity
- MHS patient or relatives with adverses effects from heat & exercise
  - should limit activity

AnesthesiologyNews.com Oct 2014

Awake MH

- common findings
  - no succinylcholine or volatile gases
  - muscle rigidity, hyperthermia, CVS collapse, & positive MH RYR1 gene mutation
- 6 y.o. playing in splash pool on hot day
  - lower extremity rigidity, trismus, temperature 108.9 F
  - fulminant MH reaction transferred to ER
    - given succinylcholine to intubate & died
      - always defer succinylcholine for intubation in hyperthermic patient

Pediatric Anesthesia.2013;23:851

Case Presentation

- 2 y.o. Female 12.7 kg for dental restorations
  - MHS family history
- TIVA GA + intubation
  - Propofol, MS, nitrous oxide, & glycopyrrolate
- 15 minutes post induction
  - hyperthermia → rapid rise temp to 41.6 C in 10 minutes
  - end tidal 52 mm despite increase in ventilation
- 28 minutes post induction
  - dantrolene 2.5 mg/kg IV + active cooling, fluids, & sodium bicarb
  - temperature started to decrease in 5 minutes
- cancelled case, extubate, transfer to hospital, discharged next day

Anesth Analg. 2010;111(3): 822

Case Presentation

- Case Review
  - machine was prepped overnight in standard fashion
  - no infection
  - cause UNDETERMINED
- "Until we understand the mechanism of human MH triggering, no anesthetic regimen can guarantee safety"

Anesthesiology.1981;54:1-2
Anesth Analg.2012;111(3): 822

Mimics of MH

- Fever but no muscle rigidity
  - sepsis, thyrotoxicosis, pheochromocytoma, iatrogenic overheating during surgery, & anticholinergic syndrome
- Fever along with muscle rigidity
  - neuroleptic malignant syndrome (NMS), cocaine, amphetamines, & ecstasy
- Osteogenesis Imperfecta

MH Susceptible Employees

- are MHS employees at risk in your office?
  - in reviewing the literature, no reports were found documenting any risk to MHS staff participating in general anesthetics using volatile agents in the office
- operatories should have proper scavenging
  - volatile gases are heavier than air and fall to ground
  - will keep gas levels to < 5 ppm

MHS Patient Recovery Time

- inpatient or ambulatory surgery
- general anesthesia without triggering agents
  - no adverse intraoperative event
- Recovery time
  - inpatient: PACU for at least 1 hour, may consider 2 hours
    - monitor vital signs Q 15 mins
  - ambulatory surgery
    - PACU for 1 hour and monitor vital signs Q 15 mins
    - Phase 2 PACU/Step down for another 1 hour
    - consider use of chemstrip to document absence of myoglobin
  - vital signs: ECG, pulse oximetry, pulse, BP, temperature, & CO_2

MHS Patients & Office Anesthesia

- is it safe to do MHS patients in the office?
  - local anesthesia & nitrous oxide are not triggers
  - TIVA agents are not triggers
  - Yes, it should be safe
  - Do I need to stock Dantrolene in the office?
  - Are there concerns?

MH Concerns in the Office

- emergency intubation for lost airway in offices without anesthesia machines & offices that just do moderate to deep sedation
  - incidence of this event → no data available
  - incidence of use of succinylcholine → no data available to assess risk
  - non depolarizing agents are an alternative

  - ***I Gel LMA would be the most appropriate airway device***

MH Concerns in the Office

- Incidence of laryngospasm in children & adults?
- Incidence of succinylcholine in these cases?
  - 7304 pediatric sedations by pediatric critical care specialists
    - 0.3% incidence of spasm
  - pediatric propofol anesthetics outside of OR by anesthesiologists
    - 0.2% incidence of spasm
  - 7581 dental pediatric anesthetics
    - 5 patients needed succinylcholine to manage spasm 0.065%
  - no current data on adults

  - Probability of needing succinylcholine for spasm is 0.03%
  - Recommendation from paper → stock dantrolene

Anesth Analg. 2013;116:118

MHS patients & Office Surgery

- If you use succinylcholine, do you need dantrolene?
- Dental literature
  - JOMS. 2008; 66: 1485-88… "until all trigger agents can be removed from an OMFS office, you need to stock 10 to 12 vials of dantrolene to give an initial dose to a 70 kg patient."
  - OOO. 2011; 112:e1-e7…. Stock 10 to 12 vials in office if you have triggering agents
- MHAUS site → stock 36 vials dantrolene or 3 vials of Ryanodex
  - remember: complications ↑ 1.6 times for every 30 minute delay from the 1st sign of MH and the use of dantrolene → 2.9 ↑ in complications for every 2° C rise in temperature

Alternatives to Succinylcholine

- Rocuronium
  - new onset laryngospasm → failed positive pressure → not "blue"
    - 0.6 mg/kg → full paralysis in ~ 2 minutes → cords sooner
  - laryngospasm → patient is "crashing"
    - 1.0 mg/kg → cord paralysis in ~ 1 minute
  - need to ventilate patient > 30 minutes
  - consider reversal with neostigmine / glycopyrrolate before you discharge patient
  - Sugamadex: encapsulates and inactivates rocuronium
    - 2-16 mg/kg: dose ≥ **4 mg/kg** reverses in < 3 minutes (1 to 2 min)
    - available in Europe not US → bronchospasm holds up FDA approval

Adlesic – Ganzberg. MH Chapter. Pending publication

Alternatives to Succinylcholine

- Lidocaine 1%
  - positive pressure fails to relieve laryngospasm
  - inject 1 to 2 ml of 1% lidocaine through the cricothyroid membrane
    - 25 gauge needle 1 – 2 ml 1% lidocaine
  - causes an immediate cough to open cords
  - cords get anesthetized by lidocaine as it is coughed out of the airway
  - reduces risk of recurrent laryngospasm

Int Anesthesiol Clin.1997;35(3): 13-31

Alternatives to Succinylcholine

- Propofol
  - study used low dose propofol for laryngospasm after LMA removal in children
  - 0.8 mg of Propofol IV
  - 752 LMA – General anesthetics
    - 20 pts had laryngospam after LMA removed
    - all got positive pressure with 100% oxygen
      - 7 of 20 responded to positive pressure
      - 13 had desaturations to 85% → got Propofol
        - 10 patients responded
        - 3 got re intubated after succinylcholine
  - proposed new study at 1 to 1.5 mg/kg in future

Paediatric Anesthesia.2002;12:625

MHS patients & Office Surgery

- MHAUS opinion if no triggers used in GA
  - no different than any ambulatory center
    - PACU for 1 hour and monitor vital signs Q 15 mins
    - Phase 2 PACU/Step down for another 1 hour
    - consider use of chemstrip to document absence of myoglobin
    - vital signs: ECG, pulse oximetry, pulse, BP, temperature, & CO_2

How long do you recovery your office anesthetics?

Anesthesia Course

- audience was asked if they used trigger agents in the office
  - 117 responded yes
  - 72 responded no
- those who used trigger agents where asked if they had dantrolene
  - 64 responded yes
    - the follow up question should have been. What trigger agent????
  - 93 responded no
- the debate continues in the dental community

Questions

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