

Clinical features

Onset of the MH in humans is extremely variable; in initial symptoms and in the time of onset of syndrome.

There have been instances where fulminant MH has occurred in patients who have previously tolerated potent triggers without difficulty. Reason is unknown.

Timing	Clinical signs	Changes in monitored variable	Biochemical changes
Early	Sustained jaw rigidity after suxamethonium Tachypnea (if SV) Rapid exhaustion of soda lime Hot soda lime canister High PR (irregular pulse)	Increase MV (SV) Rising ETCO ₂ Tachycardia (ventricular ectopics) (tented T waves on ECG)	Decreased pH hyperK
Succeeding	Patient hot to touch Cyanosis Dark blood in wound (irregular pulse)	Rising body temperature Falling SpO ₂ (ventricular ectopics) (tented T waves on ECG)	Decrease PaO ₂ hyperK
Late	Generalized muscle rigidity Prolonged bleeding Dark urine Oliguria (irregular pulse) Death	 Ventricular ectopics Tented T waves on ECG	Increased creatine kinase, myoglobinuria hyperK

Triggers and safe drugs in malignant hyperthermia

Triggers

(must be avoided)

Halothane
Enflurane
Isoflurane
Sevoflurane
Desflurane
Succinylcholine

Safe drugs

All intravenous anaesthetics including ketamine
All benzodiazepines
All non-depolarising neuromuscular blocking drugs
All local anaesthetics, including preparations containing vasoconstrictors
All analgesics, including opioids
Neostigmine
Atropine
Glycopyrrolate
Metoclopramide
Droperidol

'Safe drugs' have been evaluated in the laboratory and safely used in patients known to be susceptible to malignant hyperthermia. Other drugs used in the context of anaesthesia have not necessarily been so thoroughly tested. Readers are advised to seek expert opinion from the Leeds MH Investigation Unit should they consider using other drugs in susceptible patients.

Malignant hyperthermia

- uncommon pharmacogenetic disorder of skeletal muscle, a syndrome triggered in susceptible individual by commonly-used volatile anaesthetics + suxamethonium
- Clinical diagnosis, high mortality rate (early days 80%, recently with dantrolene + better monitoring ~ 5%)

Genetics

- autosomal dominant inheritance w/ variable penetrance + expressivity
 - only 5% of all MH showed chromosome 19 abnormalities in Ryanodine receptor on 19q13
 - Also 17, 7, and 3
 - Occurs on 2nd or later triggering anesthetic in 1/3 of cases
 - But all thought to be picked up by contracture testing
- MHS loci
 - MHS1: Ryanodine Receptor; 19q13, 50% of family and 20% of pt
 - MHS2: Na⁺ channel (SCNA4); 17q11
 - MHS3: Ca⁺⁺ channel (CACNL2A); 7q21
 - MHS4: 3q13
 - MHS5: Ca⁺⁺ channel (CACNA1S); 1q32
 - MHS6: 5p

Incidence

- General Population
 - Anywhere from 1:60,000 anaesthetics to suspected in 1:4000
- Familial
 - Most families - dominant pattern of inheritance
 - Variable penetrance and expressivity
 - Occurs on second or later triggering anaesthetic in 1/3
 - But all thought to be picked up by contracture testing
- Genetics
 - At least 4 chromosomal locations
 - Best defined is the Ryanodine receptor on 19q13
 - Also 17, 7, and 3
- Fulminant MH: overall 1:200,000 (if only cases with volatile / sux considered 1:60,000)
- Suspected MH: overall 1:16,000 (if only volatile / sux considered 1:4,000)
- Characterize by accelerated hypermetabolism
- incidence of approx 1:40,000 GA in adults and 1:15,000 in children.

Diseases Associated with Malignant Hyperthermia

RYR1 mutations have been found in 50-80% of patients and relatives who are labeled MH susceptible by positive contracture tests and in almost all families with Central Core Disease and King-Denborough syndrome.

Etiopathology

- condition is a result of a rapid accumulation of Ca in striated muscle cytoplasm due to a defect in calcium-release channel of sarcoplasmic reticulum
- \uparrow iCa stimulate metabolism both directly + indirectly
 - Directly through activation of phosphorylase to \uparrow glycolysis
 - indirectly b/c of high demand for ATP production (ATPase are important components of myofilament relaxation + Ca sequestration pumps of SR and sarcolemma)

Fig: Schematic representation of the triad junction of skeletal muscle shows the junctional foot protein (RYR1) and its associated proteins. In skeletal muscle, the α -subunit of the dihydropyridine receptor participates in excitation-contraction coupling. These physical links transmit essential signals across the narrow gap of the triadic junction that activate the RYR1 and release Ca^{2+} from the sarcoplasmic reticulum

Dantrolene

Action

- direct-acting muscle relaxant
- blocking Ca release from SR
 - neuromuscular transmission + electrical properties of skeletal muscle membrane unaffected
 - little / no effect on smooth / cardiac muscle
- total paralysis cannot be obtained (attribute to its poor water solubility)

Preparation

- lyophilized orange powder 20mg/vial + mannitol 3g (isotonicity) + NaOH (increase solutbility) – diluted with 60ml H₂O for injection
- **Incompatibilities:**
Dantrolene is incompatible with acidic solutions, including 5% dextrose injection and 0.9% sodium chloride injection.
- rate of dissolution increase by heat
- **Stability:** - After reconstitution, protect from temperatures below 15°C or above 30 °C Protect from direct light. Use within 6 hours
- Give them through blood filters (avoid problems with crystals / precipitate)
 - Precipitate formation has occurred after transfer of reconstituted dantrolene solutions to large glass bottles for preparation of an intravenous infusion. It is recommended that intravenous infusions be prepared in sterile plastic bags, immediately prior to the time of anticipated use. Also, the prepared infusion should be inspected for cloudiness and/or precipitation prior to use, and discarded if either is present.
 - Pharmacokinetics
- given ivi / PO (20% bioavailability)
- V_d ~ 1L/kg
- metabolized by liver microsomes by hydroxylation to weakly active metabolite and excreted in urine (and bile)

- T1/2b 12 hrs; clearance 1ml/kg/min

Dosage

- 2-2.5mg/kg iv every 15 mins until 10mg/kg or until sx resolved

S/E of dantrolene

- From formulation
 - Mannitol – diuresis may occur (? Good)
 - NaOH – thromboplebitis
- Side effect related to dantrolene itself
 - Skeletal muscle weakness – usually does not affect respiration / coughing
 - GI upset – nausea / vomiting / diarrhea
 - Uterine atony
 - Hepatitis + pleural effusion in chronic PO uses
 - Drug interaction (see below)

Intravenous Dantrolene & Ca blocker

- Avoid concurrent use of verapamil with iv dantrolene (shown to cause VF + CVS collapse from severe hyperK in anaesthetized swines)
- also retriggers MH
- profound myocardial depression
∴ don't use CCB concurrently with iv dantrolene in mx of a malignant hyperthermic crisis

QMH dantrolene stock:

F3 recovery room and K11 recovery room contains 6 vials for initial resuscitation.

Early additional Dantrolene should be mobilized from pharmacy (23 vials stock)