



**Innovative Option
for the Treatment
of Malignant
Hyperthermia (MH)**

Ryanodex[®]
 (dantrolene sodium)
for injectable suspension

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ABSTRACT

Malignant hyperthermia (MH) is a rare hypermetabolic reaction that can develop during any medical procedure involving succinylcholine or volatile anesthetics and constitutes a medical emergency. The standard of care is immediate discontinuation of the MH-triggering agent, suspending any ongoing surgery, implementing appropriate supportive measures, and administering IV dantrolene sodium. Delays in the administration of dantrolene sodium have been found to increase the morbidity and mortality of MH.

Dantrolene sodium has been available in the United States since 1979. Currently, there are 3 dantrolene sodium products available, resulting in differences in how the dantrolene sodium is supplied, reconstituted, and administered.

RYANODEX® (dantrolene sodium) for injectable suspension is a formulation that minimizes time delays due to product reconstitution and administration. Each 250-mg vial of RYANODEX® contains the same amount of dantrolene sodium as 12.5 vials of the 2 low-concentration high-volume products, and can be reconstituted and administered in less than 1 minute. RYANODEX® was approved on July 22, 2014, following priority review by the US Food and Drug Administration. The use of RYANODEX® in the management of a malignant hyperthermia crisis is not a substitute for previously known supportive measures. Treatment must be individualized. As soon as the MH reaction is recognized, all volatile anesthetics and succinylcholine should be discontinued; ventilation with high-concentration oxygen is recommended. Anesthesia may be maintained with intravenous anesthetic agents and opioids.

MH: AN OPERATING ROOM CRISIS

MH overview

Malignant hyperthermia (MH) is a rare, potentially fatal, hypermetabolic crisis that can occur in genetically susceptible patients exposed to MH-triggering agents and certain types of general anesthesia, including volatile anesthetics or succinylcholine.¹ MH is a medical emergency that requires immediate action, including stopping the MH-triggering agent, suspending any ongoing surgery, and rapidly treating the patient with dantrolene sodium.¹² Dantrolene sodium acts as an “antidote” by halting the crisis that characterizes MH. Based on historical data, untreated MH was fatal in 80% of cases.^{3,4} The approval of IV dantrolene sodium in 1979, combined with increased awareness and more reliable presurgical diagnosis, yield a drastic mortality reduction to about 5%.⁵ However, serious MH complications continue to occur in about 35% of MH patients.⁶

MH presents as a hypermetabolic response to MH-triggering agents: volatile anesthetic gases such as halothane, sevoflurane, and desflurane, and the depolarizing muscle relaxant succinylcholine.¹ Other anesthetic drugs do not appear to trigger MH. MH-triggering agents are inconsistent in causing an MH cascade. A susceptible individual may undergo multiple anesthetics with an MH-triggering agent without incident but still react to such agents on a subsequent occasion. A history of uneventful anesthesia with MH-triggering agents does not rule out susceptibility to MH. In those situations where the anesthesiologist is aware of an MH risk, MH-triggering agents are usually avoided.

In persons susceptible to MH, the ryanodine receptor gene 1 or other genes involved in calcium regulation are altered, resulting in excessive calcium release from the sarcoplasmic reticulum in

the presence of MH-triggering agents. This excessive calcium release results in a hypermetabolic reaction and an increase in carbon dioxide production.⁷ Additionally, MH is associated with metabolic and respiratory acidosis, accelerated oxygen consumption, heat production, activation of the sympathetic nervous system, hyperkalemia, tachypnea, disseminated intravascular coagulation (DIC), and multiorgan dysfunction. Even with treatment and survival, the patient is at risk for life-threatening complications and recrudescence of the syndrome within the first 24 to 36 hours following the episode.⁸

MH epidemiology

MH is a rare condition and is recognized as such by the National Institutes of Health Office of Rare Disease Research and the Malignant Hyperthermia Association of the United States (MHAUS). Because there are less than 200,000 cases per annum, MH qualifies as an orphan indication in the US. Estimates of its frequency are generally expressed as the number of cases per anesthesia administration because of its direct association with the administration of MH-triggering anesthetics. According to MHAUS, the exact incidence of MH is unknown but is estimated to be between 1:5000 and 1:100,000 procedures involving general anesthesia.¹⁹

MH is genetically inherited in humans in an autosomal dominant pattern; about 1:3000 people are thought to carry a ryanodine receptor 1 gene mutation, but it may be present in as many as 1:2000.¹⁹ Both a genetic predisposition and exposure to 1 or more MH-triggering agents are assumed to be necessary to evoke an MH crisis during surgery.

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MH susceptibility is a result of a genetic abnormality (there are multiple mutations); consequently, MH clusters appear in family groups. For this reason, the incidence of MH varies geographically depending on the concentration of MH families in a given area. High-incidence areas in the United States include Wisconsin, Nebraska, West Virginia, and Michigan. A complete patient and family history is necessary for a full evaluation of the chances of an MH crisis in any given patient.⁹

The incidence of an MH event is 5 times higher in children compared with adults, and children under 15 years of age account for more than half of all cases of MH.¹⁸ The severity of the disease has been shown to be greater in older children, possibly due to the higher degree of skeletal muscle growth in children during puberty.¹⁰

A link between MH and other diseases such as exertional heat stroke has been noted. In an observational study, an abnormal caffeine-halothane contraction response, which is indicative of MH susceptibility, was found in 40% of patients following an episode of exertional heat stroke. This is well above the rate seen in the general population of less than 1%, indicating possible MH-like pathophysiology in some patients with exertional heat stroke.^{11,12}

MH pathology and diagnosis

MH is difficult to diagnose in the early stages of the metabolic crisis, as the symptoms (tachycardia and a rise in end-tidal carbon dioxide) are nonspecific.¹ As the crisis progresses, other indicators such as acidosis, fever, hyperkalemia, and muscle rigidity emerge; these indicators also may have a slow onset initially but can precipitate exponentially. Later signs include myoglobinuria and organ failure. Temperature elevation may be an important confirmatory sign of MH. When it occurs, hyperthermia is marked by increasing core temperature at a rate of 1°C to 2°C every 5 minutes. Severe hyperthermia (core temperature greater than 44°C) leads to a marked increase in oxygen consumption and carbon dioxide production, widespread vital organ dysfunction, and disseminated intravascular coagulation (DIC), the usual causes of death from MH.

MH treatment

Treatment recommendations for MH are provided by the Prescribing Information for RYANODEX[®] and MHAUS, and can be broken down into 2 broad categories: the administration of dantrolene sodium and providing supportive measures. For over 3 decades, MHAUS has been operating a hotline that surgical/anesthesia staff can call for treatment guidance during an MH crisis.¹³

Supportive measures: Supportive measures required during an MH crisis involve correcting the effects of the hypermetabolic state: providing hyperventilation to flush volatile anesthetics, cooling the patient, reversing acidosis and hyperkalemia, and forced diuresis to help prevent acute renal failure.¹⁴

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Administration of dantrolene sodium: Dantrolene sodium inhibits the ryanodine receptor, lessening the release of calcium into the myoplasm, and is considered an antidote to MH.¹⁵ Dantrolene sodium should be administered as an initial dose of 2.5 mg/kg (based on MHAUS recommendations) and repeated as needed. Product labeling for dantrolene sodium indicates a maximum cumulative dose of 10 mg/kg. Though MHAUS suggests no upper limit of treatment doses, it recommends considering other etiologies if doses over 10 mg/kg do not result in a response.^{2,16-18}

Prior to the introduction of dantrolene sodium, MH was fatal in about 80% of cases.^{3,4} Once MH has been diagnosed, the time taken to the provision of dantrolene sodium is a prime determinant of patient outcome.

Time to deliver dantrolene sodium: Multiple researchers have found a direct relationship between time to dantrolene sodium administration and the incidence of MH complications and death.^{5,6}

- Larach et al emphasize the importance of rapid therapeutic intervention in their finding that “the likelihood of MH complications increases 2.9 times for every 2°C increase in maximal temperature and 1.6 times for every 30-minute delay in dantrolene sodium administration.”⁶
- In their review of 129 MH cases in Canada, Riazi et al further refine the relationship between time to treatment and patient outcome: “Complications occurred in 20.1% of patients, the most common complication being renal dysfunction. When 20 or more minutes between the first adverse sign and dantrolene sodium treatment elapsed, complication rates increased to 30% or greater.”⁵ The importance of early administration of dantrolene sodium in reducing morbidity is further underlined by the findings that when dantrolene sodium administration was delayed beyond 50 minutes, the complication rate increased to 100%.
- Statistical analyses of data from the NAMHR (North American Malignant Hyperthermia Registry) from 1992 through 2012 showed that every 15-minute delay in the time to dantrolene sodium administration was associated with an increased risk of complication or death of 7.8%.¹⁹ It is important to note that diagnostic delays are not considered an element of time to dantrolene sodium administration.

Overview of dantrolene sodium IV products

There are currently 3 IV dantrolene sodium products available in the United States.¹⁶⁻¹⁸ Dantrium[®] IV and Revonto[®] supply dantrolene sodium in 20-mg vials, each of which contains 3000 mg of mannitol.^{17,18} Both of these products require reconstitution with 60 mL of sterile water for injection and must form a solution prior to administration. The most recently approved dantrolene sodium product, RYANODEX[®], can be administered as a nanoparticle suspension. This allows RYANODEX[®] to be supplied at a higher concentration with a lower volume and less mannitol. Each vial of RYANODEX[®]

is reconstituted with just 5 mL of sterile water and contains 250 mg dantrolene sodium and only 125 mg of mannitol. Additionally, a pharmacokinetic study in healthy volunteers found that RYANODEX® had a faster T_{max} and higher C_{max} when compared to Dantrium.²⁰

RYANODEX® was approved in 2014 following a priority review by the Food and Drug Administration. Table 1 summarizes differences in formulations of IV dantrolene sodium products available in the United States.

Table 1. Comparison of IV dantrolene sodium products for a 250-mg loading dose

	Low-concentration high-volume products ^{17,18}	RYANODEX® ¹⁶
Amount of dantrolene sodium per vial	20 mg	250 mg
Preparation and administration of a 250-mg loading dose		
Reconstitution & administration time	>15 minutes ²¹	Less than 1 minute ²²
Sterile water for injection	750 mL	5 mL
Staff needed²³	2 or more	1
Mannitol administered*	37,500 mg	125 mg
Diluent	Sterile water for injection (without bacteriostatic agent)	Sterile water for injection (without bacteriostatic agent)
Concentration of dantrolene sodium following reconstitution	20 mg/60 mL (0.33 mg/mL)	250 mg/ 5mL (50 mg/mL)
pH	-9.5 Care must be taken to prevent extravasation of dantrolene sodium solution into the surrounding tissues due to the high pH of the intravenous formulation and potential for tissue necrosis	-10.3 Care must be taken to prevent extravasation of RYANODEX® into the surrounding tissues due to the high pH of the intravenous formulation and potential for tissue necrosis
FDA approval	Dantrium IV – September 1979 Revonto – July 2007	July 2014

*When mannitol is used in the prevention or treatment of late renal complications of MH, the 3000 mg of mannitol in each 20-mg vial of Dantrium or Revonto should be taken into consideration. RYANODEX® does not contain a sufficient amount of mannitol to induce and maintain a level of diuresis.

Potential complications of dantrolene sodium administration

Fluid load: Excess fluid load can be an immediate problem for patients with significant cardiovascular, pulmonary, or renal conditions, and complicates the MH management process. Sixty (60) mL of sterile water for injection is required to solubilize the contents of each vial of the low-concentration high-volume dantrolene sodium products.^{17,18} At 2.5 mg/kg, a 100-kg patient will receive 750 mL of sterile water with the loading dose. A maximum labeled dose of 10 mg/kg would require 3 liters of sterile water to be administered. This is a highly significant volume of fluid to bolus administer.

Fluid and electrolyte imbalances: All formulations of IV dantrolene sodium contain mannitol. Because of its low molecular weight, mannitol is freely filtered through the renal tubules.²⁴ However, as it is not reabsorbed, it continues to be osmotically active in the tubules. This accounts for its action as an osmotic diuretic. Mannitol also causes release of renal prostaglandins that lead to renal vasodilation and an increase in tubular urine flow that is believed to protect against renal injury by reducing tubular obstruction.

Mannitol has many side effects, including initial volume expansion (increasing the risk of heart failure); subsequent hypovolemia and hypotension; metabolic acidosis; and electrolyte imbalance, including hypernatremia and hypokalemia.²⁴ In large doses, it can also cause renal failure because of intrarenal vasoconstriction and intravascular volume depletion. Repeated administration may result in unacceptably high serum osmolality (320-mOsm liter) and subsequent neurological complications.

Low-concentration high-volume dantrolene sodium products contain 3000 mg of mannitol per 20-mg dantrolene sodium vial, whereas RYANODEX® contains just 125 mg of mannitol per 250-mg vial.¹⁶⁻¹⁸ Of course, the difference is much larger when considering the number of vials needed to treat a patient. For example, for a 100-kg patient, a 2.5-mg/kg loading dose would require administration of 12.5 vials of low-concentration high-volume dantrolene sodium products or 1 vial of RYANODEX®. Thus, the 100-kg patient would receive 37,500 mg of mannitol when administered a low-concentration high-volume product vs just 125 mg using RYANODEX®. This large amount of mannitol has potential to cause significant fluid shifts as described above. RYANODEX®, which provides less than 1% of the amount of mannitol contained in other products, may be less likely to cause such mannitol-related adverse effects.¹⁶ Regardless of the product used, the mannitol content administered, or lack thereof, should be considered when evaluating the diuresis needs of an MH patient.

Pain on administration and phlebitis: Pain on administration, phlebitis, or other complications of tissue irritation have been reported for many years after the administration of intravenous dantrolene sodium and are in part caused by the highly alkaline

nature of the formulation.^{15,25} In patient reports received by NAMHR from 1989 to 2012, pain on administration was reported as frequently as was independently reported infiltration of the IV fluid containing dantrolene sodium.²⁵ When the intravenous fluid containing dantrolene sodium went outside the vein in an upper extremity, there was obvious swelling. Weakness was noted in 1 of the cases in which IV infiltration was noted. Of 2 cases in which bilateral upper extremity thrombophlebitis was noted, 1 reported bilateral deep vein thrombosis and cellulitis. Cellulitis also followed phlebitis in another case. Venous thrombosis and cellulitis are complications that could extend hospital stay and can be life-threatening.

Clinical distinctions between dantrolene sodium products

Dantrolene sodium is a life-saving medication and has greatly improved the outcomes of MH crises since its availability. However, the time and staff needed to prepare low-concentration high-volume formulations of dantrolene sodium are factors that potentially limit effectiveness. These formulations may lead to treatment delays of 15 to 30 minutes before a full therapeutic dose is administered. RYANODEX[®], which can be reconstituted and administered in less than 1 minute, may have the potential to improve outcomes. Additionally, due to the low volume of sterile water required and insignificant mannitol content, it has potential to lessen the risk complications associated with dantrolene sodium administration. RYANODEX[®] has not been studied head to head with other formulations.¹⁶

MH preparedness

The National Center for Health Statistics estimated that between 2004 and 2006, a total of 53.3 million surgical and nonsurgical procedures were performed annually during 34.7 million ambulatory surgery visits; 57.2% (19.9 M) of visits occurred in hospitals and 42.8% (14.9 M) in freestanding facilities.²⁶

The relative unpredictability of an MH crisis means that institutional preparation for such an emergency is paramount.²⁷ Of course, this includes a complete presurgical patient evaluation and staff preparation, but it also means that, in the unlikely event of an MH crisis, timely administration of the correct dantrolene sodium bolus dose is essential to minimize morbidity and mortality associated with MH.^{5,6,19}

MHAUS currently recommends the contents of an MH cart include at least 36 vials of Dantrium or Revonto or 3 vials of RYANODEX[®], sufficient sterile water for injection to reconstitute multiple 60-mL vials, large-volume syringes, and administration equipment, and that the contents be available for all anesthetizing locations within 10 minutes of a decision to treat for MH. All facilities, including ambulatory surgery centers and offices, where MH-triggering anesthetics

(isoflurane, desflurane, sevoflurane, enflurane, halothane, and succinylcholine) are administered should stock dantrolene sodium, along with the other drugs and devices necessary to treat an MH reaction.²⁸ If MH-triggering agents are in use, dantrolene sodium must be accessible within 10 minutes of the declaration of an MH crisis.

Risk of medication errors

Errors in the operating room are an ongoing problem for hospitals and ambulatory surgery centers. Anything that increases the level of complication during a surgical procedure worsens this problem. In the case of MH, the requirements for product preparation and administration have the potential to expose patients to further risk from the MH crisis. They also add a degree of complication to what is happening in the OR and create an environment that can result in additional risk of error.

An MH cart should contain adequate dantrolene sodium to treat a case of MH in a patient representative of the geographical region (ie, geographical areas that represent patients with a high average basal metabolic index (BMI) may need to stock more than the standard recommendations), enough sterile water to reconstitute the dantrolene sodium, syringes to perform the reconstitution, and other contents as recommended by MHAUS.²⁸ If low-concentration high-volume dantrolene sodium is used, 36 vials should be stocked on the cart along with enough sterile water to reconstitute them, which is over 2 L, plus multiple syringes and needles to have multiple persons reconstituting the product during the MH crisis. Having a bag of 2 L sterile water for injection creates a significant additional risk for the patient if accidentally administered in place of another intravenous fluid. Serious patient harm can result when sterile water is administered by direct IV infusion due to hemolysis related to the hypotonic nature of the product.²⁹ Stocking only 3 vials of RYANODEX[®] and just 15 mL of sterile water would ensure the same amount of dantrolene sodium is available, but with a reduction in stock of more than 2 L of sterile water, eliminating the potential for the harm from inadvertent administration of liters of free water.

In its 2007 MEDMARX report, the US Pharmacopeia noted that surgical patients face an increased risk of harmful medication errors throughout the surgery process due to a lack of comprehensive oversight of medications.³⁰ The report summarized medication errors in outpatient surgery, the preoperative holding area, the operating room, and the postanesthesia care unit, revealing that 5% of the 11,000 records examined resulted in harm. A 2008 presentation by Steelman, based on 2006 MEDMARX data, discussed the causes of and factors contributing to operating room medication errors.³¹ MEDMARX is a registry of adverse drug events, with over 400 healthcare facilities participating in the data-gathering process.

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The following were among causes identified^{30,31}:

- Performance issues
- Communication
- Institutional drug distribution system
- Packaging container design
- Verbal orders

The following were identified in the MEDMARX database as additional contributing factors³⁰:

- Distractions in the operating room
- Staffing issues/experience
- Increased workload
- An emergency situation
- No 24-hour pharmacy available to support OR needs

Risks specific to ambulatory surgery centers

Ambulatory surgery centers (ASCs) and surgical office settings in which general anesthesia is administered are growing in popularity but are often not equipped to deal with MH using dantrolene sodium, despite the existing standards of bodies that accredit ASCs.

Between 2004 and 2009, the number of Medicare-certified ASCs increased by 28%, growing from 4106 to 5260, and is at 5319 as of June 2016.^{32,33} As the number of ASCs grows, they gain significant market share across all procedures. This trend is likely to continue as both cost pressures and surgical demand rise.

Rosero et al have estimated the mortality of MH at 19.8% in patients transferred from an ASC or medical office to a hospital and 13.6% in patients transferred from a smaller or rural hospital to a larger hospital center.³⁴ This fact is especially important in light of the fact that the number of such nonhospital facilities is growing, increasing the potential risk to patients. In combination with data from Riazi et al, which demonstrated a $\geq 30\%$ increase in complications when dantrolene sodium treatment was delayed by 20 minutes, the importance of stocking dantrolene sodium at all ASCs is highlighted.

While all hospital operating rooms have MH carts available nearby, this is not always the case for all ASCs, office-based medical practices where surgery is performed, and dental/oral surgery practices where MH trigger anesthetics are employed. Some ASCs and the like may stock minimal quantities of dantrolene (for example, one 20-mg vial), which are not sufficient to treat an MH crisis. Rather, during a crisis, they may rely on emergency transport to a hospital, delaying the time for the patient to receive a therapeutic dose. Additionally, some ASCs may choose not to stock dantrolene at all, a decision that requires them to not stock trigger agents either, to remain certified by Centers for Medicare and Medicaid Services (CMS). This produces its own risk, as succinylcholine may be required to treat certain life-threatening events during surgery.

Important Safety Information

Indications

RYANODEX[®] (dantrolene sodium) for injectable suspension is indicated for the treatment of malignant hyperthermia in conjunction with appropriate supportive measures, and for the prevention of malignant hyperthermia in patients at high risk.

Important Safety Information

RYANODEX[®] is not a substitute for appropriate supportive measures in the treatment of malignant hyperthermia (MH), including discontinuing use of MH-triggering anesthetic agents, managing the metabolic acidosis, instituting cooling when necessary, and administering diuretics to prevent late kidney injury due to myoglobinuria (the amount of mannitol in RYANODEX[®] is insufficient to maintain diuresis).

RYANODEX[®] is associated with skeletal muscle weakness such as loss of grip strength and weakness in the legs, as well as drowsiness, dizziness, dysphagia, dyspnea, and decreased inspiratory capacity. Patients should not be permitted to ambulate without assistance until they have normal strength and balance. Care must be taken to prevent extravasation of RYANODEX[®] into the surrounding tissue due to the high pH of the reconstituted RYANODEX[®] suspension and potential for tissue necrosis.

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CONCLUSIONS

The discovery and clinical development of dantrolene sodium was a watershed occasion for anesthesia because it provided a solution to a rare but significant problem: malignant hyperthermia. When MH was recognized as a clinical entity in the late 1960s, mortality was about 80%.^{3,4} The approval of Dantrium in 1979, combined with increased awareness and more reliable presurgical diagnosis, yield a drastic mortality reduction to about 5%.^{3,3} However, serious MH complications continue to occur in about 35% of MH patients.⁶

The preparation and administration of low-concentration high-volume dantrolene sodium has been known to be a difficult and time-consuming process since its launch more than 30 years ago. Recent research has shown that the risk of MH complications rises directly as the time from the first sign of MH to dose administration increases. Additional clinical management issues are presented by the large doses of mannitol included in Dantrium and Revonto, and the large volume of sterile water for injection required to deliver each dose.^{17,18}

RYANODEX[®] is a formulation of dantrolene sodium that, through its technology, addresses deficiencies of other dantrolene sodium products. With RYANODEX[®], MH patients can receive the initial dose of dantrolene sodium within 1 minute, which may help minimize complications due to treatment delays, reduce pain and inflammation upon administration, and reduce the risk of complications due to large fluid volume and mannitol dose delivered.¹⁶⁻¹⁸ When treating an MH crisis, RYANODEX[®] is not a substitute for previously known supportive measures. It is vital that the following appropriate supportive measures are instituted: Discontinue use of MH-triggering anesthetic agents (ie, volatile anesthetic gases and succinylcholine), manage the metabolic acidosis, institute cooling when necessary, and administer diuretics to prevent late kidney injury due to myoglobinuria (the amount of mannitol in RYANODEX[®] is insufficient to maintain diuresis).

KEY TAKEAWAYS

- MH is a rare but serious hypermetabolic disorder that occurs in susceptible persons following exposure to volatile anesthetics or succinylcholine.
- MH requires administration of dantrolene sodium in conjunction with appropriate supportive measures.
- Delays in the administration of dantrolene sodium worsen patient outcomes.
- There are 3 dantrolene sodium products in the United States.
 - Revonto[®] and Dantrium IV are low-concentration high-volume formulations supplied in 20-mg vials, each needing to be reconstituted with 60 mL of sterile water for injection
 - RYANODEX[®] is supplied in 250-mg vials needing to be reconstituted with 5 mL of sterile water
- Because it is administered as a suspension, RYANODEX[®] takes only 10 seconds to be reconstituted and can be administered by 1 healthcare provider in 1 minute.
- Many of the potential complications of dantrolene sodium administration are secondary to the volume of sterile water for injection administered as well as the mannitol content, both of which are reduced with RYANODEX[®].

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