Current State of Malignant Hyperthermia And the Use of Dantrium IV as Treatment

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From the Bench to the Bedside

The Science Behind Positive Patient Outcomes

Introduction
Malignant hyperthermia (MH) exemplifies how the combination of clinical observation and laboratory science can lead to the identification, clarification, and improvement of patient care of an uncommon but potentially fatal disorder. MH is an autosomally inherited disorder characterized by an increase in heart rate, respiratory rate, body temperature, and muscle rigidity when the patient is exposed to potent volatile anesthetic gases (eg, halothane, sevoflurane, desflurane) and succinylcholine, a muscle relaxant.

Prevalence
The onset of MH is unpredictable and the course of action is variable. Although anywhere from 500 to 800 cases of the syndrome are reported to the Malignant Hyperthermia Association of the United States (MHAUS) each year,2,3 the prevalence and incidence of MH are difficult to determine because patients display no characteristic signs until anesthetized with one of the triggering agents, and even then do not always develop the disorder.4 Based on the most recent study, the incidence of MH is 1 in 100,000 patients.4 Despite the rarity of this syndrome, the mortality rate was once as high as 80%.5 Overall, the mortality rate has decreased to less than 10%;6 however, a recent study showed that patients who develop MH in a non-hospital setting (eg, an office or ambulatory surgical center) have a higher mortality rate than those developing MH in a hospital setting (19.8% vs 13.6%, respectively).5

Pathophysiology and Genetics of MH
Although there are pathognomonic clinical signs,7 a patient susceptible to MH will experience an increase in metabolism as a result of a rapid and uncontrolled increase in calcium within the muscle cells.8,9 Failure to regulate the calcium channels will cause the muscles to contract and increase the breakdown of adenosine triphosphate, resulting in significant heat production.10 Other changes include muscle rigidity, acidosis, muscle membrane breakdown leading to rhabdomyolysis, and release of cellular potassium.11 Consequently, the patient can experience hyperthermia, cardiac arrhythmias, or death.9

Genetic predisposition for MH is indicated in 1 of 3,000 individuals.20 Studies indicate that patients susceptible to MH have mutations within the calcium channel receptor–ryanodine receptor 1 (RyR1) gene—causing the uncontrolled release of calcium from the sarcoplasmic reticulum.1,11,12 RyR1 mutations proven to be causal for MH have been found in at least 25% of patients susceptible to the syndrome.1,11 About 50% of patients susceptible to MH will display other mutations whose significance is not yet determined.14 Patients can be tested for MH using the caffeine–halothane contracture test, which determines the contractile properties of the skeletal muscle when exposed to caffeine and halothane (ie, RyR1 agonists).1,15 Recently, DNA analysis of the RyR1 gene has been introduced as a clinical diagnostic test for MH susceptibility under specific circumstances.17 However, because DNA testing is not highly sensitive, further research is required before it becomes standard practice in diagnosing MH susceptibility.

Treatment of MH
Initial treatment of MH requires immediate recognition of associated symptoms and removal of the triggering agent.5 With the introduction of Dantrium IV (dantrolene sodium for injection), a skeletal muscle relaxant, patients with MH have an effective treatment that binds to RyR1 receptors to block the release of calcium.18,19 Patients with MH from 65 centers in the United States and Canada were enrolled in a 20-month study to assess the efficacy of dantrolene sodium in humans.16 Of the 21 patients treated with dantrolene sodium, 11 recovered without recrudescence.20 A recommended dose of 1 mg/kg every 4 to 8 hours for 24 to 48 hours is effective in regulating the calcium channels in the sarcoplasmic reticulum.21 Although 2.5 mg/kg of dantrolene sodium is the recommended dose by MHAUS,16 some patients may require a higher dose,7 as noted in a case report in which a 6-year-old child weighing 25 kg required a dose of 42 mg/kg.20 Dantrolene sodium preparation requires 60 mL of sterile water to dissolve a 20-mg vial.22 If the average dose for treatment of MH is 2.5 mg/kg, this means that for an average 70–kg patient, 9 vials of dantrolene are needed (2.5 mg × 70/20 mg per vial). However, many adults are much heavier than 70 kg. Given that some patients may need 10 mg/kg for treatment, it has been recommended that 36 vials be on hand (10 mg × 70/20 mg per vial). The number of vials needed based on patient weight and potential dosing are provided in the Table below.20

When Dantrium IV (dantrolene sodium for injection) was developed in 1979, it included sodium hydroxide and mannitol in order to stabilize the drug, but was available only in a dried, powder form. Dantrolene sodium was packaged in a 20-mg vial requiring reconstitution with 60 mL of non-bacteriostatic water. It took about 1 to 2 minutes to mix and draw up each vial of the drug.22 In 2007, US World Meds introduced the generic formulation of dantrolene sodium. Administering dantrolene sodium proved to be challenging because the agent was poorly soluble and multiple vials needed to be reconstituted for effective treatment.23 Studies also have indicated that, despite acute treatment of the MH crisis, recrudescence occurred in about 20% of cases.23 This has been shown to be related to the muscular build of the patient, temperature increases during the episode, and extended amount of time from induction to the onset of the syndrome.23 Because MH can progress to a life-threatening situation within a few moments, this was less than optimal. Recommendations were developed to guide clinicians on how to administer dantrolene sodium for injection: The recommended dose is 1 mg/kg and should be continued until symptoms subside or the maximum cumulative dose of 10 mg/kg has been reached.20

In September 2009, a more rapidly soluble form of Dantrium® IV was FDA-approved that reduces the time needed for reconstitution. Now Dantrium® IV reconstitutes in approximately 20 seconds—4 times faster than the earlier version of the agent.23 A separate unblinded study

| TABLE. Number of Vials of Dantrium® IV (20 mg/vial) Needed to Treat an MH Crisis |
|--------------------------------|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| kg Weight | lb | 1 mg/kg | 2.5 mg/kg | 5 mg/kg | 7.5 mg/kg | 10 mg/kg |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| 45               | 99              | 2.3             | 5.6               | 11.3            | 16.9            | 22.5            |
| 58               | 128             | 2.9             | 7.3               | 14.5            | 21.8            | 29.0            |
| 73               | 161             | 3.7             | 9.1               | 18.3            | 27.4            | 36.5            |
| 88               | 194             | 4.4             | 11.0              | 22.0            | 33.0            | 44.0            |
| 103              | 227             | 5.2             | 12.9              | 25.8            | 38.6            | 51.5            |
| 118              | 260             | 5.9             | 14.8              | 29.5            | 44.3            | 59.0            |
| 133              | 293             | 6.7             | 16.6              | 33.3            | 49.9            | 66.5            |
| 148              | 326             | 7.4             | 18.5              | 37.0            | 55.5            | 74.0            |

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by 4 independent observers compared older and new Dantrium® IV with regard to reconstitution time, time of transfer, and withdrawal time (Figure 1).24 A mean reconstitution time of 12.1 seconds was reported with the new Dantrium® IV. The packaging for the new Dantrium® IV has also been modified to reduce the time necessary for reconstitution. A red flip-off cap has been added to permit rapid opening of the vial, and a vacuum has been added to each vial to facilitate the entry of the diluent (non-bacteriostatic water) into the vial (Figure 2). All of these changes are significant and permit rapid mixing of Dantrium® IV. Dantrium® IV continues to have a shelf life of 36 months.23 In October 2009, Health Canada approved the rapidly mixing Dantrium® IV for the Canadian market.

**Resources**

Although much has been learned about the clinical presentation and management of MH, the rarity of this syndrome poses the concern that overall awareness may be lacking among anesthesiologists, patients, and their families. In the United States, MHAUS was established to provide clinicians and individuals with MH a support network and resource through which they can obtain the most effective approaches to patient care.25 Through its Web site (www.mhaus.org), newsletters, and numerous educational programs, MHAUS has been a driving force in educating clinicians, encouraging research studies to improve diagnostic testing and treatment, and creating awareness.25 Additionally, the North American Malignant Hyperthermia Registry (NAMHR) was established to provide a database of information derived from actual clinical episodes of MH.26 The NAMHR data have been invaluable in the standardization of MH testing, the description of the different clinical presentations of MH, and the documentation of the incidence of its morbidity and mortality, as well as a better understanding of its molecular genetics. Studies using the NAMHR database have documented the incidence of mortality and morbidity of MH, as well as the molecular genetics of the syndrome.27 In 1995, the NAMHR merged with MHAUS to form an organization that could provide the latest data and educational developments, while continuing to emphasize patient advocacy.

**Conclusion**

With the introduction of Dantrium® IV along with dissemination of educational material and a better understanding of the clinical presentation and management of MH, the mortality rate has decreased significantly over the past few decades. Early administration of dantrolene sodium for injection in adequate doses is required to treat MH successfully. As minimally invasive diagnostic testing becomes more sensitive and available, it is anticipated that patients at risk will be identified prior to being exposed to the triggering agents, leading to fewer episodes of MH and eliminating disability and mortality from this syndrome.

For further information, please contact MHAUS via its Web site, www.mhaus.org, or call (607) 674-7901. MHAUS is a not-for-profit organization.

**References**


**Figure 1.** Comparison of Dantrium® IV Blue label vs Red label.

**Figure 2.** Dantrium® IV (dantrolene sodium for injection).

For more information about Dantrium® IV please visit www.dantrium.com.