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

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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.[1]

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.[1] 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%.[4] Overall, the mortality rate has decreased to less than 10%[5]; 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).[6]

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[7] and increase the breakdown of adenosine triphosphate, resulting in significant heat production.[7,8] Other changes include muscle rigidity, acidosis, muscle membrane breakdown leading to rhabdomyolysis, and release of cellular potassium.[6] Consequently, the patient can experience hyperthermia, cardiac arrhythmias, or death.[9]

Genetic predisposition for MH is indicated in 1 of 3,000 individuals.[10] 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.[1,13] 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.[7] 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.[9] 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. 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.[16] 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.[17] Although 2.5 mg/kg of dantrolene sodium is the recommended dose by MHAUS,[18] 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.[19] Dantrolene sodium preparation requires 60 mL of sterile water to dissolve a 20-mg vial.[9] 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.[5,21] 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.[7] Studies also have indicated that, despite acute treatment of the MH crisis, recrudescence occurred in about 20% of cases.[22] 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.[22] 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]

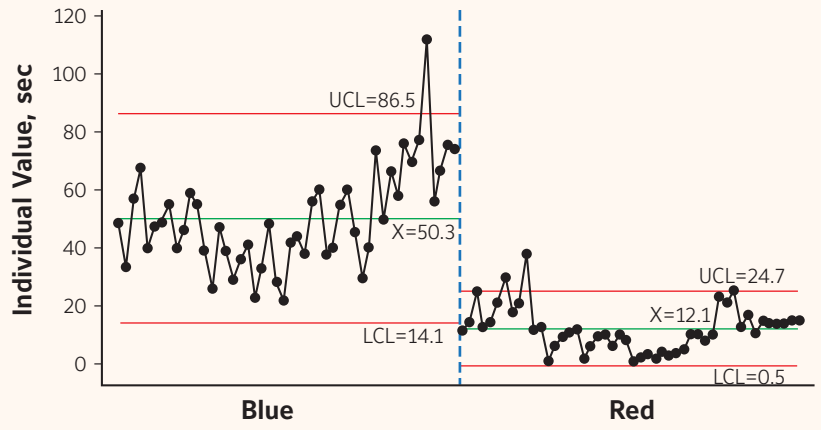
In September 2009, a more rapidly soluble form of Dantrium® IV was FDA-approved that reduces the time needed for reconstitution. Now Dantrium® IV reconstitutes in approximately 20 seconds–4 times faster than the earlier version of the agent.[23] A separate unblinded study

Table. Number of Vials of Dantrium® IV (20 mg/vial) Needed to Treat an MH Crisis

Patient Weight		Number of Vials to Achieve Dantrium Dose of:				
kg	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

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.

FIGURE 1. Comparison of Dantrium® IV Blue label vs Red label.



Blue = old; Red = new

LCL, lower control limit; **UCL,** upper control limit

FIGURE 2. Dantrium® IV (dantrolene sodium for injection).

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

Management of Malignant Hyperthermia (MH) crises requires various supportive measures individualized for the patient's condition. Administration of Dantrium® IV is one component of therapy and should not be considered a substitute for these measures. Even when properly treated, an MH crisis can result in death. Adverse events with Dantrium® IV include loss of grip strength, weakness in the legs, drowsiness, dizziness, thrombophlebitis, and tissue necrosis/injection site reactions secondary to extravasation. There have been rare reports of pulmonary edema, urticaria, and erythema. Please see accompanying full prescribing information for Dantrium® IV.

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 anesthesia providers, 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 and mortality from MH,[3] as well as the molecular genetics of the syndrome.[12] 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.

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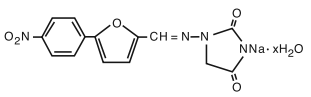
Dantrium® Intravenous

(dantrolene sodium for injection)

DESCRIPTION: **Dantrium Intravenous** is a sterile, non-pyrogenic, lyophilized formulation of dantrolene sodium for injection. **Dantrium Intravenous** is supplied in 70 mL vials containing 20 mg dantrolene sodium, 3000 mg mannitol, and sufficient sodium hydroxide to yield a pH of approximately 9.5 when reconstituted with 60 mL sterile water for injection USP (without a bacteriostatic agent).

Dantrium is classified as a direct-acting skeletal muscle relaxant. Chemically, **Dantrium** is hydrated 1-[[[5-(4-nitrophenyl)-2-furanyl]methylene]amino]-2,4-imidazolidinedione sodium salt. The structural formula for the hydrated salt is:



The hydrated salt contains approximately 15% water (3-1/2 moles) and has a molecular weight of 399. The anhydrous salt (dantrolene) has a molecular weight of 336.

CLINICAL PHARMACOLOGY: In isolated nerve-muscle preparation, **Dantrium** has been shown to produce relaxation by affecting the contractile response of the muscle at a site beyond the myoneural junction. In skeletal muscle, **Dantrium** dissociates the excitation-contraction coupling, probably by interfering with the release of Ca++ from the sarcoplasmic reticulum. The administration of intravenous **Dantrium** to human volunteers is associated with loss of grip strength and weakness in the legs, as well as subjective CNS complaints (see also PRECAUTIONS, Information for Patients). Information concerning the passage of **Dantrium** across the blood-brain barrier is not available.

In the anesthetic-induced malignant hyperthermia syndrome, evidence points to an intrinsic abnormality of skeletal muscle tissue. In affected humans, it has been postulated that "triggering agents" (e.g., general anesthetics and depolarizing neuromuscular blocking agents) produce a change within the cell which results in an elevated myoplasmic calcium. This elevated myoplasmic calcium activates acute cellular catabolic processes that cascade to the malignant hyperthermia crisis.

It is hypothesized that addition of **Dantrium** to the "triggered" malignant hyperthermic muscle cell reestablishes a normal level of ionized calcium in the myoplasm. Inhibition of calcium release from the sarcoplasmic reticulum by **Dantrium** reestablishes the myoplasmic calcium equilibrium, increasing the percentage of bound calcium. In this way, physiologic, metabolic, and biochemical changes associated with the malignant hyperthermia crisis may be reversed or attenuated. Experimental results in malignant hyperthermia susceptible swine show that prophylactic administration of intravenous or oral dantrolene prevents or attenuates the development of vital sign and blood gas changes characteristic of malignant hyperthermia in a dose related manner. The efficacy of intravenous dantrolene in the treatment of human and porcine malignant hyperthermia crisis, when considered along with prophylactic experiments in malignant hyperthermia susceptible swine, lends support to prophylactic use of oral or intravenous dantrolene in malignant hyperthermia susceptible humans. When prophylactic intravenous dantrolene is administered as directed, whole blood concentrations remain at a near steady state level for 3 or more hours after the infusion is completed. Clinical experience has shown that early vital sign and/or blood gas changes characteristic of malignant hyperthermia may appear during or after anesthesia and surgery despite the prophylactic use of dantrolene and adherence to currently accepted patient management practices. These signs are compatible with attenuated malignant hyperthermia and respond to the administration of additional i.v. dantrolene (see DOSAGE AND ADMINISTRATION). The administration of the recommended prophylactic dose of intravenous dantrolene to healthy volunteers was not associated with clinically significant cardiorespiratory changes.

Specific metabolic pathways for the degradation and elimination of **Dantrium** in humans have been established. Dantrolene is found in measurable amounts in blood and urine. Its major metabolites in body fluids are 5-hydroxy dantrolene and an acetylamino metabolite of dantrolene. Another metabolite with an unknown structure appears related to the latter. **Dantrium** may also undergo hydrolysis and subsequent oxidation forming nitrophenylfuroic acid.

The mean biologic half-life of **Dantrium** after intravenous administration is variable, between 4 to 8 hours under most experimental conditions. Based on assays of whole blood and plasma, slightly greater amounts of dantrolene are associated with red blood cells than with the plasma fraction of blood. Significant amounts of dantrolene are bound to plasma proteins, mostly albumin, and this binding is readily reversible.

Cardiopulmonary depression has not been observed in malignant hyperthermia susceptible swine following the administration of up to 7.5 mg/kg i.v. dantrolene. This is twice the amount needed to maximally diminish twitch response to single supramaximal peripheral nerve stimulation (95% inhibition). A transient, inconsistent, depressant effect on gastrointestinal smooth muscles has been observed at high doses.

INDICATIONS AND USAGE: **Dantrium Intravenous** is indicated, along with appropriate supportive measures, for the management of the fulminant hypermetabolism of skeletal muscle characteristic of malignant hyperthermia crises in patients of all ages. **Dantrium** Intravenous should be administered by continuous rapid intravenous push as soon as the malignant hyperthermia reaction is recognized (i.e., tachycardia, tachypnea, central venous desaturation, hypercarbia, metabolic acidosis, skeletal muscle rigidity, increased utilization of anesthesia circuit carbon dioxide absorber, cyanosis and mottling of the skin, and, in many cases, fever).

Dantrium Intravenous is also indicated preoperatively, and sometimes postoperatively, to prevent or attenuate the development of clinical and laboratory signs of malignant hyperthermia in individuals judged to be malignant hyperthermia susceptible.

CONTRAINDICATIONS: None.

WARNINGS: The use of **Dantrium Intravenous** in the management of malignant hyperthermia crisis is not a substitute for previously known supportive measures. These measures must be individualized, but it will usually be necessary to discontinue the suspect triggering agents, attend to increased oxygen requirements, manage the metabolic acidosis, institute cooling when necessary, monitor urinary output, and monitor for electrolyte imbalance.

Since the effect of disease state and other drugs on **Dantrium** related skeletal muscle weakness, including possible respiratory depression, cannot be predicted, patients who receive i.v. **Dantrium** preoperatively should have vital signs monitored.

If patients judged malignant hyperthermia susceptible are administered intravenous or oral **Dantrium** preoperatively, anesthetic preparation must still follow a standard malignant hyperthermia susceptible regimen, including the avoidance of known triggering agents. Monitoring for early clinical and metabolic signs of malignant hyperthermia is indicated because attenuation of malignant hyperthermia, rather than prevention, is possible. These signs usually call for the administration of additional i.v. dantrolene.

PRECAUTIONS:

General: Care must be taken to prevent extravasation of **Dantrium** solution into the surrounding tissues due to the high pH of the intravenous formulation and potential for tissue necrosis.

When mannitol is used for prevention or treatment of late renal complications of malignant hyperthermia, the 3 g of mannitol needed to dissolve each 20 mg vial of i.v. **Dantrium** should be taken into consideration.

Information for Patients: Based upon data in human volunteers, perioperatively, it is appropriate to tell patients who receive **Dantrium Intravenous** that symptoms of muscle weakness should be expected postoperatively (i.e. decrease in grip strength and weakness of leg muscles, especially walking down stairs). In addition, symptoms such as "lightheadedness" may be noted. Since some of these symptoms may persist for up to 48 hours, patients must not operate an automobile or engage in other hazardous activity during this time. Caution is also indicated at meals on the day of administration because difficulty swallowing and choking has been reported. Caution should be exercised in the concomitant administration of tranquilizing agents.

Hepatotoxicity seen **with Dantrium Capsules:** **Dantrium** (dantrolene sodium) has a potential for hepatotoxicity, and should not be used in conditions other than those recommended. Symptomatic hepatitis (fatal and non-fatal) has been reported at various dose levels of the drug. The incidence reported in patients taking up to 400 mg/day is much lower than in those taking doses of 800 mg or more per day. Even sporadic short courses of these higher dose levels within a treatment regimen markedly increased the risk of serious hepatic injury. Liver dysfunction as evidenced by blood chemical abnormalities alone (liver enzyme elevations) has been observed in patients exposed to **Dantrium** for varying periods of time. Overt hepatitis has occurred at varying intervals after initiation of therapy, but has been most frequently observed between the third and twelfth month of therapy. The risk of hepatic injury appears to be greater in females, in patients over 35 years of age, and in patients taking other medication(s) in addition to **Dantrium** (dantrolene sodium). **Dantrium** should be used only in conjunction with appropriate monitoring of hepatic function including frequent determination of SGOT or SGPT.

Fatal and non-fatal liver disorders of an idiosyncratic or hypersensitivity type may occur with **Dantrium** therapy.

Drug Interactions: **Dantrium** is metabolized by the liver, and it is theoretically possible that its metabolism may be enhanced by drugs known to induce hepatic microsomal enzymes. However, neither phenobarbital nor diazepam appears to affect **Dantrium** metabolism. Binding to plasma protein is not significantly altered by diazepam, diphenylhydantoin, or phenylbutazone. Binding to plasma proteins is reduced by warfarin and clofibrate and increased by tolbutamide.

Cardiovascular collapse in association with marked hyperkalemia has been reported in patients receiving dantrolene in combination with calcium channel blockers. It is recommended that the combination of intravenous dantrolene sodium and calcium channel blockers, such as verapamil, not be used together during the management of malignant hyperthermia crisis.

Administration of dantrolene may potentiate vecuronium-induced neuromuscular block.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Sprague-Dawley female rats fed **Dantrium** for 18 months at dosage levels of 15, 30, and 60 mg/kg/day showed an increased incidence of benign and malignant mammary tumors compared with concurrent controls. At the highest dose level (approximately the same as the maximum recommended daily dose on a mg/m2 basis), there was an increase in the incidence of benign hepatic lymphatic neoplasms. In a 30-month study in Sprague-Dawley rats fed dantrolene sodium, the highest dose level (approximately the same as the maximum recommended daily dose on a mg/m2 basis) produced a decrease in the time of onset of mammary neoplasms. Female rats at the highest dose level showed an increased incidence of hepatic lymphangiomas and hepatic angiosarcomas.

The only drug-related effect seen in a 30-month study in Fischer-344 rats was a dose-related reduction in the time of onset of mammary and testicular tumors. A 24-month study in HaM/ICR mice revealed no evidence of carcinogenic activity.

The significance of carcinogenicity data relative to use of **Dantrium** in humans is unknown.

Dantrolene sodium has produced positive results in the Ames S. Typhimurium bacterial mutagenesis assay in the presence and absence of a liver activating system.

Dantrolene sodium administered to male and female rats at dose levels up to 45 mg/kg/day (approximately 1.4 times the maximum recommended daily dose on a mg/m2 basis) showed no adverse effects on fertility or general reproductive performance.

Pregnancy: Pregnancy Category C: **Dantrium** has been shown to be embryocidal in the rabbit and has been shown to decrease pup survival in the rat when given at doses seven times the human oral dose. There are no adequate and well-controlled studies in pregnant women. **Dantrium Intravenous** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: In one uncontrolled study, 100 mg per day of prophylactic oral **Dantrium** was administered to term pregnant patients awaiting labor and delivery. Dantrolene readily crossed the placenta, with maternal and fetal whole blood levels approximately equal at delivery; neonatal levels then fell approximately 50% per day for 2 days before declining sharply. No neonatal respiratory and neuromuscular side effects were detected at low dose. More data, at higher doses, are needed before more definitive conclusions can be made.

Nursing Mothers: Dantrolene has been detected in human milk at low concentrations (less than 2 micrograms per mL) during repeat intravenous administration over 3 days. Because of the potential for serious adverse reactions in nursing infants from dantrolene, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Geriatric Use: Clinical studies of **Dantrium Intravenous** did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS: There have been occasional reports of death following malignant hyperthermia crisis even when treated with intravenous dantrolene; incidence figures are not available (the pre-dantrolene mortality of malignant hyperthermia crisis was approximately 50%). Most of these deaths can be accounted for by late recognition, delayed treatment, inadequate dosage, lack of supportive therapy, intercurrent disease and/or the development of delayed complications such as renal failure or disseminated intravascular coagulopathy. In some cases there are insufficient data to completely rule out therapeutic failure of dantrolene.

There are reports of fatality in malignant hyperthermia crisis, despite initial satisfactory response to i.v. dantrolene, which involve patients who could not be weaned from dantrolene after initial treatment.

The administration of intravenous **Dantrium** to human volunteers is associated with loss of grip strength and weakness in the legs, as well as drowsiness and dizziness.

The following adverse reactions are in approximate order of severity:

There are rare reports of pulmonary edema developing during the treatment of malignant hyperthermia crisis in which the diluent volume and mannitol needed to deliver i.v. dantrolene possibly contributed.

There have been reports of thrombophlebitis following administration of intravenous dantrolene; actual incidence figures are not available. Tissue necrosis secondary to extravasation has been reported.

There have been rare reports of urticaria and erythema possibly associated with the administration of i.v. **Dantrium**. There has been one case of anaphylaxis.

Injection site reactions (pain, erythema, swelling), commonly due to extravasation, have been reported.

None of the serious reactions occasionally reported with long-term oral **Dantrium** use, such as hepatitis, seizures, and pleural effusion with pericarditis, have been reasonably associated with short-term **Dantrium Intravenous** therapy.

The following events have been reported in patients receiving oral dantrolene: aplastic anemia, leukopenia, lymphocytic lymphoma, and heart failure. (See package insert for **Dantrium** (dantrolene sodium) **Capsules** for a complete listing of adverse reactions.)

The published literature has included some reports of **Dantrium** use in patients with Neuroleptic Malignant Syndrome (NMS). **Dantrium Intravenous** is not indicated for the treatment of NMS and patients may expire despite treatment with **Dantrium Intravenous**.

For medical advice about adverse reactions contact your medical professional. To report SUSPECTED ADVERSE REACTIONS, contact JHP at 1-866-923-2547 or MEDWATCH at 1-800-FDA-1088 (1-800-332-1088) or http://www.fda.gov/medwatch/.

OVERDOSAGE: Because **Dantrium Intravenous** must be administered at a low concentration in a large volume of fluid, acute toxicity of **Dantrium** could not be assessed in animals. In 14-day (subacute) studies, the intravenous formulation of **Dantrium** was relatively non-toxic to rats at doses of 10 mg/kg/day and 20 mg/kg/day. While 10 mg/kg/day in dogs for 14 days evoked little toxicity, 20 mg/kg/day for 14 days caused hepatic changes of questionable biologic significance.

Symptoms which may occur in case of overdose include, but are not limited to, muscular weakness and alterations in the state of consciousness (e.g., lethargy, coma), vomiting, diarrhea, and crystalluria.

For acute overdosage, general supportive measures should be employed.

Intravenous fluids should be administered in fairly large quantities to avert the possibility of crystalluria. An adequate airway should be maintained and artificial resuscitation equipment should be at hand. Electrocardiographic monitoring should be instituted, and the patient carefully observed. The value of dialysis in **Dantrium** overdose is not known.

DOSAGE AND ADMINISTRATION: As soon as the malignant hyperthermia reaction is recognized, all anesthetic agents should be discontinued; the administration of 100% oxygen is recommended. **Dantrium Intravenous** should be administered by continuous rapid intravenous push beginning at a minimum dose of 1 mg/kg, and continuing until symptoms subside or the maximum cumulative dose of 10 mg/kg has been reached.

If the physiologic and metabolic abnormalities reappear, the regimen may be repeated. It is important to note that administration of **Dantrium Intravenous** should be continuous until symptoms subside. The effective dose to reverse the crisis is directly dependent upon the individual's degree of susceptibility to malignant hyperthermia, the amount and time of exposure to the triggering agent, and the time elapsed between onset of the crisis and initiation of treatment.

Pediatric Dose: Experience to date indicates that the dose of **Dantrium Intravenous** for pediatric patients is the same as for adults.

Preoperatively: **Dantrium Intravenous** and/or **Dantrium Capsules** may be administered preoperatively to patients judged malignant hyperthermia susceptible as part of the overall patient management to prevent or attenuate the development of clinical and laboratory signs of malignant hyperthermia.

Dantrium Intravenous: The recommended prophylactic dose of **Dantrium Intravenous** is 2.5 mg/kg, starting approximately 1-1/4 hours before anticipated anesthesia and infused over approximately 1 hour. This dose should prevent or attenuate the development of clinical and laboratory signs of malignant hyperthermia provided that the usual precautions, such as avoidance of established malignant hyperthermia triggering agents, are followed.

Additional **Dantrium Intravenous** may be indicated during anesthesia and surgery because of the appearance of early clinical and/or blood gas signs of malignant hyperthermia or because of prolonged surgery (see also CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS). Additional doses must be individualized.

Oral Administration of Dantrium Capsules: Administer 4 to 8 mg/kg/day of oral **Dantrium** in three or four divided doses for 1 or 2 days prior to surgery, with the last dose being given with a minimum of water approximately 3 to 4 hours before scheduled surgery. Adjustment can usually be made within the recommended dosage range to avoid incapacitation (weakness, drowsiness, etc.) or excessive gastrointestinal irritation (nausea and/or vomiting). See also the package insert for **Dantrium Capsules.**

Post Crisis Follow-Up: **Dantrium Capsules**, 4 to 8 mg/kg/day, in four divided doses should be administered for 1 to 3 days following a malignant hyperthermia crisis to prevent recurrence of the manifestations of malignant hyperthermia.

Intravenous **Dantrium** may be used postoperatively to prevent or attenuate the recurrence of signs of malignant hyperthermia when oral **Dantrium** administration is not practical. The i.v. dose of **Dantrium** in the postoperative period must be individualized, starting with 1 mg/kg or more as the clinical situation dictates.

PREPARATION: Each vial of **Dantrium Intravenous** should be reconstituted by adding 60 mL of sterile water for injection USP (without a bacteriostatic agent), and the vial shaken until the solution is clear. 5% Dextrose Injection USP, 0.9% Sodium Chloride Injection USP, and other acidic solutions are not compatible with **Dantrium Intravenous** and should not be used. The contents of the vial must be protected from direct light and used within 6 hours after reconstitution. Store reconstituted solutions at controlled room temperature (59°F to 86°F or 15°C to 30°C).

Reconstituted **Dantrium Intravenous** should not be transferred to large glass bottles for prophylactic infusion due to precipitate formation observed with the use of some glass bottles as reservoirs.

For prophylactic infusion, the required number of individual vials of **Dantrium Intravenous** should be reconstituted as outlined above. The contents of individual vials are then transferred to a larger volume sterile intravenous plastic bag. Stability data on file at JHP Pharmaceuticals indicate commercially available sterile plastic bags are acceptable drug delivery devices. However, it is recommended that the prepared infusion be inspected carefully for cloudiness and/or precipitation prior to dispensing and administration. Such solutions should not be used. While stable for 6 hours, it is recommended that the infusion be prepared immediately prior to the anticipated dosage administration time.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

HOW SUPPLIED: **Dantrium Intravenous** (**NDC** 42023-123-06) is available in vials containing a sterile lyophilized mixture of 20 mg dantrolene sodium, 3000 mg mannitol, and sufficient sodium hydroxide to yield a pH of approximately 9.5 when reconstituted with 60 mL sterile water for injection USP (without a bacteriostatic agent).

Store unreconstituted product at controlled room temperature (59°F to 86°F or 15°C to 30°C) and avoid prolonged exposure to light.

Rx only.

Prescribing Information as of November 2008

JHP PHARMACEUTICALS
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