PRODUCT MONOGRAPH

Pr Dantrolene Sodium for Injection, USP

Sterile Lyophilized Powder for Solution for Injection

20 mg / vial

Skeletal Muscle Relaxant

Hikma Canada Limited
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20 mg/vial

ACTION: Dantrolene sodium is a muscle relaxant acting specifically on skeletal muscles. In isolated muscle preparations, dantrolene sodium uncouples the excitation and contraction of skeletal muscles, probably by interfering with the release of calcium from the sarcoplasmic reticulum. In the anesthetic induced malignant hyperthermia syndrome, evidence points to a predisposing intrinsic abnormality of muscle tissue. In affected humans, it has been postulated that "triggering agents" induce a sudden rise in myoplasmic calcium either by preventing the sarcoplasmic reticulum from accumulating calcium adequately, or by accelerating its release. This rise in myoplasmic calcium activates acute catabolic processes common to the malignant hyperthermia crisis.

Dantrolene sodium may prevent the increase in myoplasmic calcium and the acute catabolism within the muscle cell by interfering with the release of calcium from the sarcoplasmic reticulum to the myoplasm. Thus, the physiologic, metabolic and biochemical changes associated with the crisis may be reversed or attenuated.

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. 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.

In humans dantrolene metabolism is rapid via hepatic microsomal enzymes. The major metabolites in body fluids are the 5 hydroxy analog and the acetylamino analog. Dantrolene also undergoes a minor metabolic pathway of hydrolysis and subsequent oxidation to form nitrophenylfuroic acid. Urinary excretion of dantrolene and its metabolites occurs in an initially rapid phase (t-1/2, 2.5 to 3 hours) followed by a slower phase over a 24-hour period. Dantrolene sodium is also removed by biliary excretion and through the feces. The mean biologic half-life of dantrolene sodium after intravenous administration is about 5 hours.

Based on limited information obtained from study patients with malignant hyperthermia, it is estimated that therapeutic efficacy of the drug is obtained at a serum concentration of dantrolene of about 1 mcg/mL. No toxic effects have been observed in humans with malignant hyperthermia up to a dose level of 10 mg/kg with serum dantrolene concentrations up to 13.79 mcg/mL.

INDICATIONS AND CLINICAL USE: Dantrolene Sodium for Injection, USP is indicated in the management of malignant hyperthermia crisis. As soon as the crisis is recognized (i.e., tachycardia, tachypnea, central venous desaturation, central venous hypercarbia, metabolic acidosis, fever, skeletal muscle rigidity or cyanosis and mottling of the skin) cooling procedures should be instituted and Dantrolene Sodium for Injection, USP administered. If anesthetic agents are being administered they should be promptly discontinued. It is also important that appropriate supportive measures be instituted for treatment of the physiologic and metabolic abnormalities. Dantrolene sodium for injection, when given early in the malignant hyperthermia crisis, has caused abrupt lowering of body temperature, correction of the respiratory and/or metabolic acidosis, decrease of the heart rate, stabilization of blood pressure, and disappearance of the rigidity and/or fasciculations. Patients who received dantrolene sodium for injection during the crisis had less evidence of muscle destruction as

shown by serum creatinine phosphokinase measurements than those treated by other measures.

CONTRAINDICATIONS: There are no known contraindications when Dantrolene Sodium for Injection, USP is used during an acute malignant hyperthermia crisis.

WARNINGS: General: The use of Dantrolene Sodium for Injection, USP 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 dantrolene sodium related skeletal muscle weakness, including possible respiratory depression, cannot be predicted, patients who receive intravenous dantrolene sodium preoperatively should have vital signs monitored.

If patients judged malignant hyperthermia susceptible are administered intravenous or oral dantrolene sodium 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 intravenous dantrolene sodium.

Because of the high pH of the intravenous formulation of Dantrolene Sodium for Injection, USP and potential for tissue necrosis, care must be taken to prevent extravasation of the intravenous solution into the surrounding tissues.

When mannitol is used for prevention or treatment of renal complication of malignant hyperthermia, the 3 g of mannitol needed to dissolve each 20 mg vial of intravenous dantrolene sodium should be taken into consideration.

Information for Patients: Based upon data in human volunteers, it will sometimes be appropriate to tell patients who receive intravenous dantrolene sodium that decrease in grip strength and weakness of leg muscles, especially walking down stairs, can be expected postoperatively. 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 have been reported. Caution should be exercised in the concomitant administration of tranquilizing agents.

Hepatic: Hepatic dysfunction, including fatal hepatic failure, can occur with dantrolene use, and is related to dose and duration of therapy.

Hepatotoxicity seen with dantrolene sodium capsules: 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

doses 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 dantrolene sodium for varying periods of time. Overt hepatitis has occurred at varying intervals after initiation of therapy, but has been most frequently observed between the second and twelfth month of therapy. The risk of hepatic injury appears to be greater in females, in patients over 30 years of age, and in patients taking other medication(s) in addition to dantrolene sodium. Dantrolene sodium 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 dantrolene sodium therapy.

PRECAUTIONS: Pregnancy and Lactation: The safety of Dantrolene Sodium for Injection, USP in women who are or who may become pregnant has not been established; Dantrolene crosses the placenta, and should be given only when the potential benefits have been weighed against the possible risk to mother and child. Dantrolene has been detected in human milk at low concentrations (less than 2 micrograms per milliliter) during repeat intravenous administration over 3 days. Dantrolene Sodium for Injection, USP should be used by nursing mothers only if the potential benefit justifies the potential risk to the infant.

Animal Data: In rabbits receiving 45 mg/kg/day during the period of organogenesis, there was a statistically significant increase in the frequency of pelvic ribs. In rats receiving 20 mg/kg/day there was an increased frequency of pelvic ribs, and in rats receiving 60 mg/kg/day there was suppression of fetal weight.

Effects on Ability to Drive and Use Machines: Dantrolene causes dizziness, drowsiness, and weakness. Patients should be cautioned regarding operating a motor vehicle or participating in hazardous occupations after receiving dantrolene.

DRUG INTERACTIONS: Dantrolene sodium 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 dantrolene sodium 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.

The combination of therapeutic doses of intravenous dantrolene sodium and verapamil in halothane/α-chloralose anesthetized swine has resulted in ventricular fibrillation and cardiovascular collapse in association with marked hyperkalemia. Hyperkalemia and myocardial depression have been observed in malignant hyperthermia-susceptible patients receiving intravenous dantrolene and concomitant calcium channel blockers. It is recommended that the combination of intravenous dantrolene sodium and calcium channel blockers, such as verapamil, not be used during the reversal of a malignant hyperthermia crisis.

Administration of dantrolene may potentiate vecuronium-induced neuromuscular block.

ADVERSE REACTIONS: The more serious reactions reported with repeated doses of oral dantrolene sodium as a muscle relaxant have been hepatitis, seizures and pleural effusions with pericarditis. Cases of fatal hepatitis have been reported in patients who had received dantrolene sodium for sixty days or longer. Symptomatic hepatitis and laboratory evidence of liver dysfunction have also been reported in a number of patients receiving dantrolene

sodium as a muscle relaxant. Acneiform skin reactions have also been infrequently reported. For a list of adverse reactions reported with the use of dantrolene sodium as a muscle relaxant, please consult the appropriate Product Monograph (dantrolene sodium capsules – use as a muscle relaxant). None of these reactions have been reported during clinical trials in patients treated with short-term intravenous dantrolene sodium therapy for malignant hyperthermia.

There have been occasional reports of death following malignant hyperthermia crisis even when treated with intravenous dantrolene sodium; 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 sodium.

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

The administration of intravenous dantrolene sodium to human volunteers is associated with loss of grip strength and weakness in the legs, as well as subjective central nervous system complaints (see Information for Patients under **WARNINGS**).

There have been reports of the effects listed below by systems following administration of intravenous dantrolene sodium:

Cardiovascular System: thrombophlebitis, injection site reactions
Digestive System: choking, difficulty swallowing
Integumentary System: erythema (rare), urticaria (rare)
Musculoskeletal System: loss of grip strength, muscular weakness
Nervous System: lightheadedness
Respiratory System: pulmonary edema (rare) (diluent volume and mannitol needed to deliver intravenous dantrolene may contribute to the event)

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health- canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

SYMPTOMS AND TREATMENT OF OVERDOSAGE:

For management of a suspected drug overdose, contact your regional poison control centre immediately.

There is no known constellation of symptoms with acute overdose. Drowsiness and generalized muscle weakness have been reported following very large doses of oral dantrolene sodium and would be expected as the major symptoms of overdosage. Other symptoms, which may occur in case of overdose include, but are not limited to 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 made available. Electrocardiographic monitoring should be instituted, and the patient carefully observed. No experience has been reported with dialysis; hence its value in dantrolene sodium overdosage is not known.

DOSAGE AND ADMINISTRATION:

Note: When oral administration of dantrolene sodium is considered, a Product Monograph for dantrolene sodium capsules should be consulted.

During the crisis: As soon as the malignant hyperthermia reaction is recognized, all anesthetic agents should be discontinued. Dantrolene Sodium for Injection, USP 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 Dantrolene Sodium for Injection, USP 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.

Children's dose: Experience to date indicates that the dose for children is the same as for adults.

Preoperatively: If after suitable evaluation of the patient, including family history relative to malignant hyperthermia, it is felt that a malignant hyperthermia crisis may develop during anesthesia and surgery, oral dantrolene sodium may be used prophylactically 1-2 days prior to surgery. Dantrolene sodium capsules should be given at a dose of 1-2 mg/kg four times per day up to 3-5 hours prior to surgery.

The following criteria may be used as a general guideline in assessing which individuals are likely to be most susceptible to development of a malignant hyperthermia crisis during anesthesia or surgery:

1. Patients who have survived a malignant hyperthermia crisis or have a positive muscle biopsy.
2. A first-degree relative of anyone known to be malignant hyperthermia

susceptible or to have a positive muscle biopsy.

3. A member of a suspected family who has a clinically demonstrable muscle abnormality.
4. A member of a suspected family whose plasmas CPK value has been found elevated in one or more samples (tested on at least three occasions).

Post Crisis Follow-up: Dantrolene sodium capsules should also be administered following a malignant hyperthermia crisis in doses of 4 to 8 mg/kg per day in four divided doses, for a one- to three-day period to prevent recurrence of the manifestations of malignant hyperthermia.

Unreconstituted Dantrolene Sodium for Injection, USP vials: Store at controlled room temperature (20°C to 25°C) and protected from light.

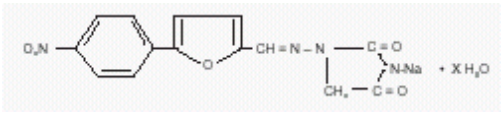
Reconstitution: Each vial of Dantrolene Sodium for Injection, USP should be reconstituted by adding 60 mL of sterile water for injection USP (without a bacteriostatic agent), and the vial shaken until the solution is clear. **Store reconstituted solution between 15 to 30°C, protected from light. The reconstituted solution must be used within 6 hours after reconstitution.**

AVAILABILITY: Dantrolene Sodium for Injection, USP is available in 100 mL vials with Bromobutyl (FM257/2) stoppers, the vial stoppers are not made with natural rubber latex. Each vial contains a sterile lyophilized mixture of 20 mg dantrolene sodium, 3,000 mg mannitol, and sufficient sodium hydroxide to yield a pH of approximately 9.5 when reconstituted. These are single dose vials. Available in cartons of 6 vials.

Dantrolene Sodium for Injection, USP is available only for use in hospitals or in dental clinics that are equipped to provide the necessary supportive measures used in the treatment of the malignant hyperthermia crisis.

Dantrolene Sodium for Injection, USP is a Schedule F (prescription only) drug.

PHARMACOLOGY: Dantrolene Sodium, 1- {[5-(p-nitrophenyl)-furturylidene]amino}-hydantoin sodium hydrate, has the following structural formula:



Dantrolene sodium causes marked, dose-dependent skeletal muscle relaxation in laboratory animals with a long duration of action. The pharmacologic profile of dantrolene sodium in animals is unlike neuromuscular blocking agents in that total muscle paralysis and/or respiratory depression do not occur.

Various studies *in vivo* and *in vitro* demonstrated the apparent selectivity of action of dantrolene sodium for skeletal muscle. There were some non-specific depressant effects seen in several smooth muscle studies and insignificant effects in cardiac muscle in doses which cause skeletal muscle relaxation. Nerve transmission was not affected by dantrolene sodium in several animal studies.

Intravenous dantrolene sodium has no appreciable effect on the cardiovascular system or on respiratory function. A transient inconsistent effect on smooth muscles has been observed at high doses.

It has been shown that dantrolene sodium has no effect on the propagated action potential recorded on the muscle membrane, and the total membrane capacitance is not decreased by the drug, indicating that it does not disrupt the function of the transverse tubular system, and acts at a point beyond the electrically excitable surface membrane. Evidence obtained *in vitro* with muscle preparations exposed to caffeine, an agent known to cause muscle contractions by releasing internal Ca + + stores in muscle, suggests that dantrolene sodium acts on skeletal muscle by altering the Ca + + release mechanisms. Such an action could explain the apparent specificity of dantrolene sodium for skeletal muscle.

In dogs approximately 40% of an intravenous dose of dantrolene sodium is excreted as the hydroxylated metabolite in bile whereas only 1% of the dose is excreted in this manner by the rat. High biliary concentrations of this metabolite have also been found in the Rhesus monkey. Total excretion of known metabolites in the urine is estimated at approximately 3% in the dog and approximately 10% in the rat.

Studies with malignant hyperthermia susceptible swine have shown that in the established syndrome of malignant hyperthermia induced by halothane or succinylcholine dantrolene sodium caused:

1. Rapid loss of muscle rigor commencing within five minutes and usually complete within 20 minutes.
2. Immediate cessation of the increase in deep muscle temperature followed by a rapid decrease.
3. Termination of the progressive, inexorable acidosis characteristic of the syndrome rendering easy the buffering of acidosis developed until dantrolene sodium administration.

Survival rates with dantrolene sodium were 100% as contrasted with 40% with procaine administration. Untreated, the developed syndrome had a mortality rate of 100%. Procaine administration was associated with profound cardiovascular effects while dantrolene sodium had no effect on the myocardium, a factor that permitted the drug's use up to the limits of therapeutic effectiveness. Mean doses of dantrolene sodium used to successfully treat these animals were 7 mg/kg.

TOXICOLOGY: Because of the low drug concentration (0.5 mg/mL) requiring the administration of large volumes of fluid, acute toxicity of intravenous dantrolene sodium could not be assessed. In 14-day (subacute) studies, dantrolene sodium was relatively non-toxic to rats at doses of 10 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.

Toxicity studies in animals provided evidence of low-grade carcinogenic activity of dantrolene sodium capsules in the rat. For a full report on the results of long term toxicity studies in animals please consult the Product Monograph for dantrolene sodium capsules (use as a muscle relaxant).

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

Reproductive Toxicity: Dantrolene sodium administered to male and female rats at dose levels up to 45 mg/kg/day showed no adverse effects on fertility or general reproductive performance of adult animals.

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