Dantrium Intravenous (dantrolene sodium for injection)

**DISPOSITION:** Dantrium Intravenous is a sterile, non-pyrogenic, non-bacteriostatic drug for injection. Dantrium Intravenous is supplied in 10 mg/mL with mannitol as an osmotic agent, 20 mg/mL, and mannitol solution 0.9% with a pH of approximately 6.5 when reconstituted with sterile, water for injection (IP) as a bacteriostatic agent.

Dantrium is a direct-acting skeletal muscle relaxant. Chemically, Dantrium is 1-[5-(4-nitrophenyl)-2-isoxazolyl]dantrolene, a salt of dantrolene, with a molecular weight of 336.02. Dantrium is a white to off-white, odorless granular powder, which is practically insoluble in water, freely soluble in methanol, and slightly soluble in ethanol.

**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 neuromuscular junction. In isolated muscle, Dantrium dissociates from the muscle receptors with the release of Ca from the sarcoplasmic reticulum. The administration of intravenous Dantrium to human volunteers is associated with a loss of strength and weakness in the legs, as well as an increase in CBF (see also PRECAUTIONS, and ADVERSE REACTIONS). A transient, but consistent, depressant effect on gastrointestinal smooth muscle has been noted. Cardiopulmonary depression has not been observed in malignant hyperthermia susceptible humans. When prophylactic intravenous dantrolene is used, the administration of the recommended prophylactic dose of intravenous dantrolene to a patient may not prevent myocardial ischemia or arrhythmias if the patient is in a malignant hyperthermic crisis during surgery. The efficacy of intravenous dantrolene in the treatment of malignant hyperthermia crisis, when used prophylactically, has not been determined. The efficacy of intravenous dantrolene in the management of malignant hyperthermia crisis, when used as an emergency, has not been determined.

**INDICATIONS AND USAGE:** Use of intravenous dantrolene is indicated prophylactically in the management of malignant hyperthermia crisis. The use of intravenous dantrolene in malignant hyperthermia crisis is also indicated preoperatively, and for the treatment of malignant hyperthermia crisis in a dose-related manner. The use of intravenous dantrolene is not a substitute for previously implemented supportive measures. These measures cannot be individualized, but it is usually necessary for the patient to be on a hypercarbic carbon dioxide absorber, managed the ventilatory acid-base conditions when necessary, assure adequate vascular access, and ready for electrocution.

**CONTRAINDICATIONS:** Malignant hyperthermia is chemically a direct-acting skeletal muscle relaxant. Chemically, Dantrium is 1-[5-(4-nitrophenyl)-2-isoxazolyl]dantrolene, a salt of dantrolene, with a molecular weight of 336.02. Dantrium is a white to off-white, odorless granular powder, which is practically insoluble in water, freely soluble in methanol, and slightly soluble in ethanol.

**PRECAUTIONS:** Care must be taken in the preoperative administration of Dantrium solution into the surrounding tissue due to the high pH of the intravenous formulation and potential for tissue necrosis.

**ADVERSE REACTIONS:** Adverse reactions are not usually seen in patients receiving intravenous dantrolene in the context of malignant hyperthermia crisis. However, when intravenous dantrolene is given at a near steady state level for 3 or more hours after the infusion is completed, clinical experience has shown that early signs and/or blood gas changes characteristic of malignant hyperthermia may be delayed in their appearance and may be attenuated to the point of non-recognition or observation. In a patient with malignant hyperthermia, CNS symptoms may become apparent only after the patient has been successfully resuscitated and chemotherapy has been administered.

**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 neuromuscular junction. In isolated muscle, Dantrium dissociates from the muscle receptors with the release of Ca from the sarcoplasmic reticulum. The administration of intravenous Dantrium to human volunteers is associated with a loss of strength and weakness in the legs, as well as an increase in CBF (see also PRECAUTIONS, and ADVERSE REACTIONS). A transient, but consistent, depressant effect on gastrointestinal smooth muscle has been noted. Cardiopulmonary depression has not been observed in malignant hyperthermia susceptible humans. When prophylactic intravenous dantrolene is used, the administration of the recommended prophylactic dose of intravenous dantrolene to a patient may not prevent myocardial ischemia or arrhythmias if the patient is in a malignant hyperthermic crisis during surgery. The efficacy of intravenous dantrolene in the treatment of malignant hyperthermia crisis, when used prophylactically, has not been determined. The efficacy of intravenous dantrolene in the management of malignant hyperthermia crisis, when used as an emergency, has not been determined.

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Dantrolene sodium administered to male and female rats at dose levels up to 40 mg/kg/day (approximately 10 times the maximum recommended daily dose for a 50-kg patient) showed no evidence of adverse effects on general reproductive performance.

Preparation: Dantrolene sodium is available for oral administration as capsules containing 100, 200, or 400 mg of dantrolene sodium and as an intravenous solution containing 5 mg/mL dantrolene sodium in 60 mL of sterile water for injection USP. The solution for intravenous injection should be reconstituted with 60 mL sterile water for injection USP (without additional preservative) to a concentration of 5 mg/mL prior to administration. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Particulate matter and discoloration in the drug product indicates that the vials should not be used.

For acute overdosage, general supportive measures should be applied. Special attention should be paid to the maintenance of adequate urinary output to prevent the development of renal failure due to excessive dantrolene levels. If the patient is restless and tachycardic, attempts should be made to quieten the patient and slow heart rate. Central sympathomimetic stimulants, which have been shown to be effective in some cases, should not be used. In patients who have become hyperpyrexial and those with a rectal temperature greater than 104°F (40°C), an attempt should be made to lower body temperature by using external cooling techniques. Cooling should be effective, and any increase in the patient's temperature should be immediately reported.

During use of oral or intravenous dantrolene, patients should be carefully observed for signs and symptoms of toxicity. The physician should be prepared to institute appropriate supportive measures and equipment, including endotracheal intubation and mechanical ventilation, prior to the administration of dantrolene.

Pregnancy: Pregnancy Category C: Dantrolene sodium is not indicated for the treatment of malignant hyperthermia crisis. Unless indicated by severe muscle rigidity and weakness, the decision to use dantrolene for the development of malignan hyperthermia crisis should be based on the severity of the crisis and the likelihood of benefit. An i.m. or i.v. dose of 2.5 mg/kg, starting approximately 1 hour prior to incision or the onset of anesthesia, is recommended. Additional doses may be administered at 2-hour intervals as judged by the development of clinical and laboratory signs of malignant hyperthermia..

Dantrolene sodium administration to pregnant rats and rabbits at dose levels approximately 7 and 4 times the human oral dose, respectively, has been shown to decrease uterine contractility in rats and rabbits. In rabbits, dantrolene sodium has decreased the number of embryos, increased the number of resorbed embryos, and decreased the number of liveborn young. In rabbits, dantrolene sodium is embryocidal in the rabbit and has been shown to decrease fetal weight. In rats, dantrolene sodium has been shown to increase the number of resorbed embryos. Therefore, dantrolene sodium should not be administered to pregnant women because the potential for serious adverse reactions in nursing infants from dantrolene sodium treatment outweighs any possible benefit.

Dantrolene sodium should not be administered in the presence of probable or actual malignant hyperthermia. In these cases, the administration of dantrolene sodium should be stopped immediately, and artificial respiration, extracorporeal respiration, and hypothermia should be initiated. Dantrolene sodium is not indicated for the treatment of malignant hyperthermia crisis. Because of the risk of malignant hyperthermia, dantrolene sodium should not be administered to any patient who has been identified previously as being at risk of malignant hyperthermia.

In one uncontrolled study, 100 mg per day of dantrolene capsules and 10 mg/kg/day of intravenous dantrolene were administered to two patients with malignant hyperthermia. Neither patient developed symptoms of malignant hyperthermia during the term of the study. In general, clinical experience in patients with malignant hyperthermia has been insufficient to determine whether they respond differently from younger patients. Patients treated with dantrolene capsules tend to require higher dosages than those treated with intravenous dantrolene. Additional doses may be administered at 2-hour intervals as judged by the development of clinical and laboratory signs of malignant hyperthermia.

The following events have been reported in patients receiving oral and intravenous dantrolene: 1-800-828-9393 or FDA at 1-800-FDA-1088 or for adverse reactions to the drug. If death occurs despite treatment with intravenous dantrolene, the cause of death should be carefully documented and, if possible, the tissue(s) containing the fatal dantrolene concentration should be analyzed. Dantrolene capsules are not recommended for the treatment of malignant hyperthermia.