Dantrium Intravenous (dantrolene sodium for injection)

DESCRIPTION: Dantrium Intravenous is a sterile, non-pyrogenic, lyophilized form of dantrolene sodium for injection. After reconstitution with 60 mL of sterile water for injection USP (equivalent to 3 g of sodium dantrolene), the solution is slightly yellow to straw colored. The structural formula for the hydrated salt is:

\[
\begin{align*}
\text{CH} \quad \text{N} &= \quad \text{O} \\
\end{align*}
\]

The hydrated salt contains approximately 15%, water (5-12 mL) and a molar weight of 106. The anhydrous salt (dantrolene) has a molar weight of 336.

PHARMACOLOGICAL PROPERTY: In isolated nerve-muscle preparations, dantrolene sodium produces depression of the response to nerve excitation. This effect is concentration dependent and is antagonized by calcium. Dantrolene sodium depresses the contractile response of the muscle at a site beyond the excitation-contraction coupling, probably by interfering with the release of Ca++ from the sarcoplasmic reticulum. The administration of intravenous dantrolene to human volunteers is associated with loss of grip strength and weakness in the legs, as well as subjective complaints (see also PRECAUTIONS, Information for Patients). Information concerning the passage of dantrolene across the blood-brain barrier is not available.

In the anesthetized malignant hyperthermia syndrome, evidence points to an intrinsic abnormality of skeletal muscle tissue. These effects have been postulated that "triggering agents" (e.g., general anesthetics and depolarizing neuromuscular blocking agents) produce a change within the cell which results in a release of excessive calcium ions. An elevated myocardial calcium ion concentration enhances the increase in the drug-sensitive calcium that can occur in the malignant hyperthermia crisis. It is hypothesized that addition of dantrolene to the "triggered" malignant hyperthermic response in the skeletal muscle, which reverses a normal, an increase in the release of calcium from the sarcoplasmic reticulum by Dantrolium metabolizes the myocardial calcium equilibrium, increasing the percentage of bound calcium. In this way, physiologic, metabolic, and biochemical changes associated with the malignant hyperthermia crises may be reversed or attenuated. Experimental results in malignant hyperthermia susceptible sheep show that prophylactic administration of intravenous or oral dantrolene protects or attenuates the development of vital sign and blood gas changes characteristic of malignant hyperthermia in a dose related manner. Malignant hyperthermia is an inheritable disorder in the treatment of human and porcine malignant hyperthermia crisis, when compared to controls. These results suggest that dantrolene in malignant hyperthermia susceptible humans. When prophylactic intravenous dantrolene is administered prior to induction of a malignant hyperthermic episode, monitoring of vital signs, blood gas tensions, and electrolyte concentrations reveals a near normal state for 3 hours after the injection is completed. Clinical experience has shown that early signs and symptoms characteristic of malignant hyperthermia may appear during or after anesthesia and surgery and drug effects may be delayed. The administration of dantrolene and adherence to currently accepted patient management practices. These signs are compatible with attenuated malignant hyperthermia and is responsive 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 cardiovascular changes.

Specific metabolic pathways for the degradation and elimination of dantrolene have not been established. Dantrolene is metabolized by the liver and is thought to be sufficiently eliminated in urine. Methemoglobin has not been associated with this drug, but red blood cells with the plasma of a normal person. Since some of these symptoms may persist for up to 48 hours, patients must not operate an automobile or engage in other hazardous activities during this time. Dantrolene should be monitored for the concomitant administration of other i.v. dantrolene.

Hepatotoxic seen with Dantrium Capsules: Dantrium (dantrolene sodium) has a potential for hepatotoxicity, should not be used in conditions other than those recommended. Symptomatic hepatitis (fatal and non-fatal) has been reported at all dose levels of oral dantrolene sodium in patients taking up to 400 mg/day. In fewer than those in patients taking each daily dose within a treatment regimen markedly increased the risk of serious hepatic injury. Liver dysfunction as evidenced by blood chemical abnormalities alone (elevated serum levels of enzymes) has been reported in patients treated with Dantrolin for varying periods of time. Once hepatitis has occurred at varying intervals after initiation of therapy, has been lost frequently observed in studies lasting less than one month of therapy. The risk of hepatic injury appears to be greater in patients with altered hepatic function (e.g., in patients on other medication(s) in addition to Dantrium (dantrolene sodium)). Dantrium should be used with caution in patients with impaired monitoring of hepatic function including frequent determination of AST or ALT and 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, diphthyridine, or phenytoin. 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. In patients receiving the combination of intravenous dantrolene sodium and calcium channel blockers, such as an oral calcium blocker, together during the management of malignant hyperthermia crisis.

Administration of dantrolene may potentiate neuromuscular block. Carcinogenesis, Mutagenesis, and Impairment of Fertility: Sprague-Dawley female rats fed dantrolene for 26 months at dosage levels of 15, 30, and 60 mg/kg/day showed an increased incidence of benign and malignant mammary tumors compared with controls. Mammary tumors were observed in 27% of controls, 34% of 15 mg/kg females, 40% of 30 mg/kg females, and 62% of 60 mg/kg females. The incidence of adenocarcinomas among benign mammary tumors in the 60 mg/kg group was 13%. Hemangiosarcoma was the most frequent of these. Liver complications 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 (elevated serum levels of enzymes) has been reported in patients treated with Dantrolin for varying periods of time. Once hepatitis has occurred at varying intervals after initiation of therapy, has been lost frequently observed in studies lasting less than one month of therapy. The risk of hepatic injury appears to be greater in patients with altered hepatic function (e.g., in patients on other medication(s) in addition to Dantrium (dantrolene sodium)). Dantrium should be used with caution in patients with impaired monitoring of hepatic function including frequent determination of AST or ALT and SGPT. Fatal and non-fatal liver disorders of an idiosyncratic or hypersensitivity type may occur with Dantrium therapy.

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

Dantrium administered to male and female rats at dose levels up to 40 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 cause fetal resorptions and there has been shown to decrease pup survival in the rat when given at doses seven times the human dose of 0.7 mg/kg/day. There was no evidence of adequate and well-controlled studies in pregnant women. Dantrium Intravenous should be used during labor only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: In one uncontrolled study, 100 mg per day of Dantrium was administered to term pregnant patients allowing labor and delivery. Dantrium readily crosses the placental barrier, 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 maternal respiratory and neonatal side effects were detected at low dose. More data, at higher doses, are needed before definite conclusions can be made.

Nursing Mothers: Dantrium 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 dantrium, 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 or over to determine whether they respond differently from younger subjects. Other reported clinical trials have not identified differences in responses between the elderly and younger patients. In general, selection of an elderly patient should be governed by the same considerations as apply to selection of any patient, but geriatric patients tend to exhibit decreased renal function, decreased cardiac function, and of concomitant disease or other drug therapy that could affect the response to Dantrium Intravenous.

ADVERSE REACTIONS: There have been occasional reports due to malignant hyperthermia crisis even when treated with intravenous dantrium, incidence figures are not available (the pre-dantrolene mortality of malignant hyperthermia crisis was 50-80%).

Most of these deaths can be accounted for by late recognition, delayed treatment, inadequate dosing, lack of supportive therapy, intermittent dosing and/or the administration of non-dantrolene drugs 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 fatalities in malignant hyperthermia crisis, despite potential satisfactory response to i.v. dantrium, which involve patients who could not be weaned from dantrium after initial response.

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 drug response and mortality resulted. There have been reports of thrombophlebitis following administration of intravenous dantrium; all incidences were not associated with extravasation, have been reported. There have been rare reports of urticaria and erythema possibly associated with the administration of i.v. Dantrium. There have been case reports of anaphylaxis.

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

Some of the serious reactions occasionally reported with long-term oral Dantrium use, such as hepatitis, seizures, and oral ulceration with periapical, have been reasonably associated with short-term Dantrium therapy.

The following events have been reported in patients receiving oral dantrium: aplastic anemia, leukopenia, lymphocytopenia, lymphoma, and myeloproliferative syndrome (Please refer to insert for Dantrium (dantrolene sodium) Capsules for a complete list of adverse reactions.) There have been reports of mild exacerbation of new or pre-existing allergic skin disorders in patients using Dantrium in patients with Neutropenic Malignant Syndrome (NMS). Dantrium Intravenous is not indicated for the treatment of NMS and caution should be exercised in the treatment with Dantrium Intravenous.

For advice on adverse drug reactions contact your medical professional. To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical, Inc. at 1-800-836-6349 or 1-800-836-1868 or www.fda.gov/medwatch.

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Intravenous fluids should be administered in fairly large quantities to avert the possibility of crystallization. An adequate airway must be maintained throughout the procedure and the intravenous equipment should be hand. Electrocardiographic monitoring should be instituted, and life support measures used. The value of dialsis in dantrium overdose is not known.

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