Dantrolene Sodium Capsules

Dantrolene sodium has a potential for hepatotoxicity, and should not be used in conditions other than malignant hyperthermia. Severe hepatic failure (fulminate and fatal) has been reported in various dose levels of the drug. The incidence reported in patients taking up to 450 mg per day is three to five cases in 1000 million doses, or one case for every 200 million doses. Even at short courses of these higher dose levels, the incidence is negligible. A unique cases of a severe hepatic injury. Liver damage graded as severe by clinical and laboratory criteria on the patient has been reported in a Dantrolene sodium patient in the first month of therapy. The risk of hepatic injury appears to be greater in females, in patients with signs of liver disease (e.g., fat, cirrhosis, hepatitis C, etc.), and in patients taking other medications that are potentially hepatotoxic. In addition to dose reduction in patients with impaired liver function (see Dose and Administration), the administration of intravenous Dantrolene sodium should also include monitoring of liver enzymes to detect early signs of hepatic toxicity. In patients with known liver disease, the administration of intravenous Dantrolene sodium should be avoided.

CLINICAL PHARMACOLOGY

Dantrolene, the principal metabolite of dantrolene sodium, has been shown to produce relaxation by affecting the contractile response of the skeletal muscle and of other smooth muscle. The pharmacological effect of Dantrolene sodium is composed of a series of steps: (1) the contractile excitation contraction coupling, presumably by interfering with the release of Ca2+ from the sarcoplasmic reticulum (SR); (2) the activation of the release of Ca2+ from the SR; (3) the binding of Ca2+ to myofilaments; and (4) the inhibition of the release of Ca2+ from the SR. The result of these steps is a reduction in free intracellular Ca2+ levels and a decrease in muscle tone.

The chemical structure of dantrolene sodium is a 10-membered lactone ring with a 12-membered lactam ring. The ring is joined by two spiro carbon atoms. The lactone ring is stereoisomerically pure. It contains a tertiary amine. The lactone ring is hydrolyzed in the liver to the primary alcohol, which is then conjugated with glycine. The alcohol is further conjugated with glucuronic acid to form the glucuronide. The glucuronide is then excreted in the urine. The half-life of dantrolene sodium is approximately 10-15 hours. The half-life of the primary alcohol is approximately 2-3 hours. The half-life of the glucuronide is approximately 24-36 hours.

Dantrolene sodium is supplied in capsules of 25 mg, 50 mg, and 100 mg.

DOSAGE AND ADMINISTRATION

In Malignant Hyperthermia: Dantrolene sodium is indicated for the treatment of malignant hyperthermia and should be administered intravenously by the physician. The dosage should be increased as needed to achieve a satisfactory clinical response. The dose should be limited to no more than 4 mg/kg per dose and no more than 5 mg/kg per 24 hours. The duration of therapy should be limited to no more than 5 days.

In Chronic Spasticity: Dantrolene sodium is given orally in divided doses at intervals of 6-8 hours. The dosage should be increased as needed to achieve a satisfactory clinical response. The dose should be limited to no more than 4 mg/kg per dose and no more than 5 mg/kg per 24 hours. The duration of therapy should be limited to no more than 5 days.

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**INDICATIONS AND USAGE**

Symptoms which may occur in case of overdose include, but are not limited to, muscular weakness, feeling of suffocation, respiratory depression, chest pain, tachycardia, tachypnea, alteration of taste, increased sweating, vomiting, diarrhea, and crystalluria. For acute overdose, general supportive measures should be administered. The administration of dantrolene sodium may potentiate vecuronium-induced neuromuscular block.

**DOSAGE AND ADMINISTRATION**

**For Use in Chronic Spasticity:**

Dose selection should be based on the type and severity of spasticity, the patient’s response to therapy, and the desired therapeutic benefit. The following gradual titration schedule is suggested. Some patients will not respond to the lower doses. These lower doses may be effective in patients who are partially tolerant to dantrolene sodium.

- **25 mg once daily for seven days**
- **0.5 mg/kg once daily for seven days**
- **25 mg t.i.d. for seven days**

The most frequently occurring side effects of dantrolene sodium have been chondrocalcinosis, weakness, general malaise, fatigue, and diarrhea. These are generally transient, occurring in less than 20% of patients treated, but may persist with dosage adjustment. Chills may be severe and may be preceded by fever, sweats, headache, and malaise. They are generally transient, occurring in less than 10% of patients treated, but may persist with dosage adjustment. Chills may be severe and may be preceded by fever, sweats, headache, and malaise.

**ADVERSE REACTIONS**

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**WARNINGS**

**OVERDOSE**

Symptoms which may occur in case of overdose include, but are not limited to, muscular weakness, feeling of suffocation, respiratory depression, chest pain, tachycardia, tachypnea, alteration of taste, increased sweating, vomiting, diarrhea, and crystalluria. For acute overdose, general supportive measures should be administered. The administration of dantrolene sodium may potentiate vecuronium-induced neuromuscular block.

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