Clinical Pharmacology

In isolated nerve-muscle preparation, dantrolene sodium has been shown to produce relaxation by affecting the contractile response of the muscle at a site beyond the myoneural junction. In skeletal muscle, dantrolene sodium dissociates the excitation-contraction coupling, probably by interfering with the release of Ca++ from the sarcoplasmic reticulum. 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 CNS complaints (see also PRECAUTIONS, Information for Patients). Information concerning the passage of dantrolene sodium across the bloodbrain 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 dantrolene sodium 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 dantrolene sodium 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 dantrolene sodium 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. Dantrolene sodium may also undergo hydrolysis and subsequent oxidation forming nitrophenylfuroic acid.

The mean biologic half-life of dantrolene sodium 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.

Indications and Usage

Revonto (dantrolene sodium for injection) 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. **Revonto** 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).

Revonto 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.

Preparation

Each vial of **Revonto** (dantrolene sodium for injection) should be reconstituted by adding 60 mL of sterile water for injection USP (without a bacteriostatic agent), and the vial shaken for approximately 20 seconds or until the solution is clear. 5% Dextrose Injection USP, 0.9% Sodium Chloride Injection USP, and other acidic solutions are not compatible with Revonto 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 solution at 20-25° C (68-77° F) [see USP Controlled Room Temperature] protected from direct light. Each vial of dantrolene sodium for injection should be reconstituted by adding 60 mL of sterile water for injection USP (without a bacteriostatic agent), and the vial shaken for approximately 20 seconds or until the solution is clear.

Reconstituted **Revonto** 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 **Revonto** 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 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.

DOSING CHART

Weight of Patient		Required Number of Revonto Vials						
kg	lbs	1 mg/kg	2 mg/kg	2.5 mg/kg*	4 mg/kg	6 mg/kg	8 mg/kg	10 mg/kg
10	22	0.5	1	1.3	2	3	4	5
15	33	0.8	1.5	1.9	3	4.5	6	7.5
25	55	1.3	2.5	3.1	5	7.5	10	12.5
35	77	1.8	3.5	4.4	7	10.5	14	17.5
50	110	2.5	5	6.3	10	15	20	25
65	143	3.3	6.5	8.1	13	19.5	26	32.5
80	176	4	8	10	16	24	32	40
95	209	4.8	9.5	11.9	19	28.5	38	47.5
110	242	5.5	11	13.8	22	33	44	55
125	275	6.3	12.5	15.6	25	37.5	50	62.5
140	308	7	14	17.5	28	42	56	70
155	341	7.8	15.5	19.4	31	46.5	62	77.5
165	364	8.3	16.5	20.6	33	49.5	66	82.5

*2.5 mg/kg is the recommended prophylactic dose of Revonto. See below for additional information.

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. **Revonto** 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 **Revonto** 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 **Revonto** for pediatric patients is the same as for adults.

Preoperatively: Revonto and/or dantrolene sodium 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.

Revonto: The recommended prophylactic dose of **Revonto** is 2.5 mg/kg, starting approximately 1.25 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 **Revonto** 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 CLINCAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS). Additional doses must be individualized.

Oral Administration of Dantrolene Sodium Capsules: Administer 4 to 8 mg/kg/day of oral dantrolene sodium 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 dantrolene sodium capsules.

Post Crisis Follow-Up: Dantrolene sodium 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 dantrolene sodium may be used postoperatively to prevent or attenuate the recurrence of signs of malignant hyperthermia when oral dantrolene sodium administration is not practical. The i.v. dose of dantrolene sodium in the postoperative period must be individualized, starting with 1 mg/kg or more as the clinical situation dictates.

Do I use "actual weight" or "ideal weight" to calculate dantrolene dosing?

MHAUS regularly receives inquiries regarding the appropriate first dose administration of dantrolene. Our recommendation is a starting dose of 2.5 mg/kg intravenously based upon the patient's true weight rather than ideal weight. Although no scientific study has addressed the difference in this dosing recommendation, we believe the dosage based upon the patient's true weight would achieve a more desirable concentration of dantrolene as it redistributes from the circulatory system to the intracellular tissue spaces of skeletal muscle where its major site of action is believed to occur. Following the initial dose administration, if symptoms are not improving, continuing to administer up to 10 mg/kg is also recommended. This is not a ceiling dose, but just a guideline for initial administration. We recommend contacting the MH Hotline (1-800-644-9737) during an emergency if further guidance or consultation may be helpful.

(3) How Does The Antidote Dantrolene Work?

Dantrolene is the only currently accepted specific treatment for MH. In an episode of MH, muscle metabolism is dramatically increased secondary to an increase in calcium within the muscle. This causes muscles to contract, ATP hydrolysis, and heat production. Dantrolene directly interferes with muscle contraction; decreasing calcium in muscle cells.

Dantrolene does not block neuromuscular transmission nor interfere with reversal of muscle relaxants. Although it does not block neuromuscular transmission, the mechanical response to nerve stimulation will be depressed, with subsequent potentiation of the non-depolarizing neuromuscular blockade. When dantrolene is used with non-depolarizing muscle relaxants, care should be taken to ensure muscle strength has returned prior to extubation.

Dantrolene may cause significant muscle weakness in patients with pre-existing muscle disease and should be used with extreme caution in those patients. Sterile phlebitis may follow administration of dantrolene, and should be infused through the largest possible vein. The sterile phlebitis can be later treated with warm soaks and elevation. When used with calcium channel blockers (verapamil or diltiazem), dantrolene may produce life-threatening hyperkalemia and myocardial depression. Otherwise there does not appear to be significant negative interaction with other drugs.

Once a patient has been successfully treated for 48 hours with intravenous dantrolene may be stopped and the blood tested daily until the CK level is trending down.

How Much Dantrolene Should Be Kept On Hand?

To treat an MH episode, an initial dose of dantrolene at 2.5 mg/kg is recommended, with a suggested upper limit of 10 mg/kg. If a patient of average weight (approximately 70 kg) were to require dantrolene at the upper dosing limit, then at least 700 mg of dantrolene would be needed.

- DANTRIUM/REVONTO – stock a minimum of 36 - 20 mg vials
- RYANODEX– stock a minimum of 3 - 250 mg vials

In addition, a review of cases has shown that in a "worse case" scenario of a very large person (i.e., about 100-110 kg or 220 – 250 pounds) having an acute MH incident, as much as 8-10 mg/kg will be needed for treatment; higher doses may be requiredon rare occasions.

This regimen of dantrolene will allow for initial stabilization and treatment while more vials are being acquired to continue treatment, as needed.

Where Should Dantrolene Be Kept?

Dantrolene should be kept in or very close to the operating room, so that it is available immediately if MH occurs. Dantrolene may be stored at room temperature. A supply of sterile water for injection USP (without a bacteriostatic agent) should be kept nearby to mix with dantrolene before injection (60 ml/vial); the water for diluting dantrolene should not be stored in a refrigerator; it may be stored in a warming cabinet designed to maintain fluid temperatures between 35-40° C. All anesthesia and surgical team members should be aware of this location. NOTE: Dantrolene should not be mixed with any other diluent other than sterile water. The drug will not completely dissolve in crystalloid-containing solutions.

Should MHS Patients Be Pretreated With Dantrolene?

Dantrolene prophylaxis is not recommended for most MH-susceptible patients. Dantrolene can worsen muscle weakness in patients with muscle disease and should be used with caution. Therefore, dantrolene prophylaxis may be omitted, provided non-triggering anesthetics are used, there is appropriate monitoring, and an adequate supply of dantrolene is available.

Is dantrolene (the antidote for MH) considered safe to use in obstetrics should an MH episode occur?

While dantrolene can be given to a pregnant woman, it does cross the placenta and there are side effects in the neonate. This again is just a risk and would have to be weighed against the expected benefit. Weakness in the neonate might be expected and must be looked for and treated appropriately. An article published in 1988 suggests that at low dose, there are no problems. (Am J Obstet Gynecol., Oct 1988;159(4):831-4.