DANTROLENE

THERAPEUTICS

Brands
● Dantrium, Dantamacrin, Dantrolen

Generic?
Yes

Class
● Neuromuscular drug; skeletal muscle relaxant, direct acting

Commonly Prescribed For
(FDA approved in bold)
● Exercise-induced muscle pain
● Chronic spasticity
● Malignant hyperthermia (MT)
● Heat stroke
● Neuroleptic malignant syndrome

How the Drug Works
● Dantrolene produces relaxation by interfering with the release of calcium from the sarcoplasmic reticulum, weakening muscle contraction, and reversing the hypermetabolic process of MT

How Long until It Works
● Pain: hours–days

If It Works
● Discontinue use once MT symptoms remit. For chronic spasticity, continue to use with standard precautions

If It Doesn’t Work
● For spasticity, increase to highest tolerated dose. If ineffective, stop after 45 days and consider alternative treatments. In MT cases, stop all anesthetics

Best Augmenting Combos for Partial Response or Treatment Resistance
● For focal spasticity, e.g. post-stroke spasticity, botulinum toxin is often more effective and is better tolerated
● Use other centrally acting muscle relaxants with caution due to potential synergistic CNS depressant effect
● 100% oxygen, cold gastric lavage, cooling blankets, and cold intravenous fluids may be useful in MT

Tests
● Obtain baseline liver function studies then do periodically

ADVERSE EFFECTS (AEs)

How Drug Causes AEs
● Some are related to CNS depression, others to hepatic disease

Notable AEs
● Fatigue, diarrhea, drowsiness, weakness, rash, labile blood pressure, confusion/depression, abdominal cramps, crystalluria, chills, and fever
● Thrombophlebitis

Life-Threatening or Dangerous AEs
● Hepatotoxicity is not rare even after only short-term use, especially in patients who are females, over 35, taking multiple medications, or taking dose greater than 800 mg
● Less common: heart failure, pulmonary edema, and hematologic abnormalities have been reported

Weight Gain
● Unusual

Sedation
● Problematic

What to Do about AEs
● If symptoms of hepatotoxicity develop (clinically or based on elevated hepatic enzymes), discontinue drug. For sedation, lower the dose and titrate more slowly. Do not let patient drive or perform hazardous tasks

Best Augmenting Agents for AEs
● Most AEs cannot be improved by an augmenting agent
### DOSING AND USE

**Usual Dosage Range**
- Spasticity: 75–300 mg/day in divided doses
- MT: 1–10 mg/kg per day

**Dosage Forms**
- Capsules: 25, 50, and 100 mg
- Infusion: 20 mg/vial (with 3 g mannitol)

**How to Dose**
- Oral: start at 25 mg daily. Increase dose every 7 days and change to 3 times daily, dosing as follows: 25 mg, 50 mg, and 100 mg. Wait at least 7 days between dose increases to assess response. If increasing a dose does not produce added benefit, then decrease to the previous lower dose. For MT, give 4–8 mg/kg in 3–4 divided doses for 1–2 days before surgery. If needed following a crisis, give for 1–3 days to prevent recurrence
- Injection: preoperatively give 2.5 mg/kg about 1¼ hours before anticipated anesthesia. For recognized MT, give minimum of 1 mg/kg (usually 2) as an intravenous bolus until symptoms improve or a maximum of 10 mg/kg

**Overdose**
- Weakness, lethargy, coma, vomiting, diarrhea

**Long-Term Use**
- Safety with long-term use not established

**Habit Forming**
- No

**How to Stop**
- No need to taper

**Pharmacokinetics**
- Hepatic metabolism. Half-life of 8–9 hours on average, with peak levels at 4–5 hours
- Some drug is protein bound. Excreted in feces and urine as active drug and metabolites

**Drug Interactions**
- Use with other CNS depressants can worsen sedation
- Hepatotoxicity more common in women on oral estrogens
- Use with verapamil can cause hyperkalemia or myocardia depression
- Use with vecuronium may potentiate neuromuscular block
- Warfarin and clofibrate lower plasma protein binding of drug
- May affect concentrations of CYP3A4 medications

**Other Warnings/Precautions**
- At high doses carcinogenic in animals, although not proven in humans

**Do Not Use**
- Hypersensitivity to the drug or active hepatic disease
- Patients who rely on spasticity to sustain upright posture and balance in walking should not use

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### SPECIAL POPULATIONS

**Renal Impairment**
- No known effects

**Hepatic Impairment**
- Do not use

**Cardiac Impairment**
- May worsen existing heart failure, change blood pressure, or produce tachycardia. Use with caution

**Elderly**
- Very susceptible to AEs, including hepatotoxicity. Titrate carefully and use with extreme caution

**Children and Adolescents**
- Children over age 5 may use, but potential for carcinogenesis with long-term use. Titrate as follows: 0.5 mg/kg once daily for 7 days, then 0.5 mg/kg 3 times daily for 1 day, then 1 mg/kg 3 times daily for 1 day, then 2 mg/kg 3 times daily

**Pregnancy**
- Category C. Use only if benefits of medication outweigh risks

**Breast-Feeding**
- Do not use
**Potential Advantages**

- Most effective medication in the treatment of MT

**Potential Disadvantages**

- Multiple serious AEs, including hepatic toxicity and sedation, along with lack of long-term data make it a second-line agent for the treatment of chronic spasticity

**Primary Target Symptoms**

- Spasticity, pain, fever

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**Pearls**

- The introduction of dantrolene reduced mortality of MT from about 70% to 10%
- Drug works best for MT if given early in the setting of the illness
- The dose and usage of dantrolene for treatment of neuroleptic malignant syndrome (1 mg/kg, up to 10 mg/kg) is similar to that of acute MT, but is of unproven effectiveness

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**Suggested Reading**


