LETTERS TO THE EDITOR

Preparation of Injectable Dantrolene for Emergency Treatment of Malignant Hyperthermia-like Syndromes

DEAR SIR:

Lethal rates of metabolism are found in many exertional muscle diseases, such as malignant hyperthermia (MH), postoperative myositis, transport or capture myopathy, or azoturia. These syndromes are triggered in susceptible individuals by anesthesia, stress or exertion. A rapid rise in intramuscular calcium follows, resulting in overstimulation of metabolism and contraction. Acidosis, hyperthermia, hyperkalemia and rhabdomyolysis may follow and cause death (1-8).

Dantrolene, (1-[[5-(p-nitrophenyl)-furfurylidene] amino] hydantoin, sodium hydrate, Norwich-Eaton Pharmaceuticals) a muscle relaxant, is the only generally available drug which reverses these syndromes (1,3,4,6-8). According to the manufacturer's literature, dantrolene dissociates excitation-contraction coupling in skeletal muscle, probably by interfering with the release of Ca^{2+} from the sarcoplasmic reticulum. Supportive treatment is necessary in conjunction with dantrolene treatment, but alone will not prevent death in severe cases. Presently, veterinary usage of commercially available intravenous injectable (IV) dantrolene may be cost prohibitive. In order to have it available for emergency use during surgery on MH susceptible animals we prepared IV dantrolene from an inexpensive oral preparation, using a modification of a procedure already described (9).

The orange sodium dantrolene salt in oral capsules can be solubilized in water (1 L/g) brought to a pH of 10.3 with sodium hydroxide. After 30 min stirring, the suspension was passed through Whatman No. 1 filter paper or run through a continuous flow centrifuge to remove excipients. Centrifugation is the preferred procedure because filtration tends to be very slow, with reduced recoveries caused by extended exposure to alkaline pH. The suspension was then acidified to pH 3 with citric acid to precipitate the yellow free acid form of dantrolene (confirmed by mass spectrometry), which was filtered, washed and dried. The melting point was 279°C; yield was 72%. Since dantrolene may not be stable in solution it was stored in a dry, fine powder. Within six hours of use it was reconstituted with 10 mL of 0.088% (W/V) (sodium hydroxide per 25 mg) dantrolene and diluted 1:9 (V/V) with 5% dextrose to give a final pH of 9.5. Warming to 38°C and vigorous shaking helped dissolve the drug. Prior to injecting this solution into animals it was passed through a 0.45μ Millipore filter for sterilization and for removal of undissolved dantrolene. Therapeutic dosages reported for man, swine, horses and dogs are 3, 7.5, 2 and 1 mg dantrolene per kg, respectively (1,3-8). Reports of acute dantrolene toxicity are rare.

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Treatment of Fish Furonculosis with a Potentiated Sulfonamide Compound

DEAR SIR:

Of the many problems in fish hatcheries, one of the main diseases is caused by *Aeromonas salmonicida,* the etiological agent of fish furonculosis. In July 1982, clinical signs of the disease were found in *Salmonidae* fish of two hatcheries. Cardinal signs in the affected fish were: lethargia, inappetence, tachybronchia and hemorrhages at the base of their fins. On postmortem examination, hyperemia and scattered hemorrhages were observed over the abdominal walls and viscera. The spleen was cherry red, enlarged and with rounded edges. The intestine, empty of chyme, had a lumen usually filled with mucus and blood as far as the vent. Kidney tissue from each of the diseased fish of the two hatcheries contained *Aeromonas salmonicida.*

In one hatchery, the sulfonamide compound R05-0037[1] was used in the food (5.5 g added to each kg of food) to give each fish a dosage of about 50 mg/kg for five days, assuming that it should eat about 1% of its body weight. The diseased fishes were divided into two groups: the first one was medicated from day 1, the second group was treated from day 3, of appearance of clinical signs. In the other hatchery, the diseased fish were not medicated and served as untreated controls.

During the first nine days following medication, mortality decreased more rapidly in the group treated from day 1 than in the group treated from day 3.

[1]Hoffmann LaRoche Inc., Nutley, New Jersey 07110.