Title: Is The New Formulation of Dantrolene Sodium Quicker to Dissolve than The Old Formulation

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Introduction: Malignant hyperthermia(MH) is a potentially fatal disorder. It derives it's name from the hypermetabolic state resulting from the uncontrolled release of calcium by the ryanodine receptor into the myoplasm. The release of calcium causes uncontrolled muscle activity, exhaustion of energy reserves and development of an oxygen deficit, resulting in rhabdomyolysis, metabolic and respiratory acidosis, and hyperkalemia. The only known treatment for MH is to administer dantrolene sodium. The intravenous administration of Dantrolene sodium is hampered by the relative insolubility of the medication. The drug is received as a lyophilized powder containing 20 mg of dantrolene sodium, 3 gm of mannitol and sodium hydroxide as needed to adjust for pH in a glass vial. The medication is mixed with 60 ml of preservative free sterile water. The original formulation of dantrolene sodium was manufactured by Procter & Gamble and is currently produced by JHP Pharmaceuticals. This formulation has been previously studied and has been found to take as much as 2 minutes to dissolve at room temperature. Another brand of dantrolene sodium is produced by US WorldMeds. This company's preparation of dantrolene sodium has never been studied. We therefore sought to test the solubility of the medication and if increasing the temperature of the diluents hastened the dissolution of the drug.

M**ethods:** 10 samples of dantrolene sodium were taken from one vial of the old formulation and one vial of the new formulation of dantrolene sodium. Each sample was vigorously mixed with preservative free sterile water in vials labeled with specified time intervals of 4,8,12,16,20,24,30,40,50 seconds, and 5 min. The times reflected how long the mix was to be agitated prior to being aspirated into a 10 ml syringe. A 40 micron Millipore filter was attached to the syringe and the contents of the syringe strained through it into a vial. Three 20 microliter aliquots of each sample were pippetted into a tissue culture plate. Absorbance was subsequently read at 450 nm with a Labsystems Multiscan Plus uv/vis spectrophotometer. The mean of the absorbances from each of the 3 aliquots per sample was subsequently charted and compared.

Results: Comparison of the old formulation and the new formulation of dantrolene sodium at room temperature (23^{o}C) resulted in the old formulation dissolving quicker than the new formulation. The spectrophotometer readings indicated a higher absorbance of drug earlier and at each matched time interval. The comparison of warm diluent to room temperature diluent yielded similar results to previous studies making the same comparison. The warm diluents (40^{o}C) increased the rate of dissolution for both formulations, with the most improvement for the new formulation. The new formulation at 40^{o}C experienced 'instantaneous" dissolution within 4 seconds. Comparison of the drug concentrations at 50 seconds as compared to 5 minutes demonstrated that near complete dissolution occurred for the 40^{o}C groups for both old and new formulations. A surprising finding was that at room temperature, the new formulation did not approach near complete dissolution at 50 seconds as compared to the old.

Dantrolene Specimen	Absorbance (450 nm) at time 4 sec	8 sec	12 sec	16 sec	20 sec	24 sec	30 sec	40 sec	50 sec	5 min
Old Formulation (rm temp)	2.575	2.599	2.632	2.663	2.647	2.676	2.699	2.717	2.733	2.985
New Formulation (rm temp)	2.243	2.479	2.508	2.525	2.531	2.546	2.556	2.616	2.687	3.114
Old Formulation (40 deg Celsius)	2.867	2.886	2.945	2.983	3.064	3.062	3.042	3.066	3.041	3.092
New Formulation (40 deg Celsius)	3.1	3.134	3.117	3.134	3.274	3.205	3.099	3.014	3.162	3.197

Discussion: The successful treatment of a malignant hyperthermia episode in a patient requires quick recognition and administration of dantrolene sodium. The standard bolus dose of dantrolene sodium is 2.5 mg/kg. In a 70 kg patient this =175 mg of dantrolene sodium=9 vials of dantrolene sodium. In order to ensure the shortest delivery time, the use of warm diluent seems prudent. However, the manufacturer of dantrolene sodium has released a statement indicating the warming of diluents may affect the effectiveness of the drug. This remains an area for further investigation. By measuring absorbance as a way of determining concentration of dissolved dantrolene, we were able to show that the new formulation of dantrolene appears to take longer to fully dissolve as compared to the old formulation. However, by mixing with water heated to 40 deg Celsius, the dissolution of the new formulation was almost instantaneous. This prompts the question of whether warming affects effectiveness of dantrolene.

References:

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