An Evidence Based Comparison and Decision Making Algorithm for the use of Ryanodex Formulation Versus Traditional Dantrolene

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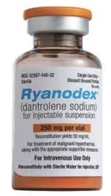

Objective

The purpose of this study is to examine current evidence and compare the outcomes of malignant hyperthermia (MH) patients following administration of either Ryanodex or standard dantrolene, in order to develop a decision making algorithm for safe and cost efficient treatment.

Introduction

Malignant hyperthermia (MH) is an autosomal dominant pharmacogenetic muscle disorder triggered by halogenated volatile anesthetics and the depolarizing neuromuscular blocker, succinylcholine, both commonly used in general anesthesia (Just et al., 2015). Historically, MH during or after general anesthesia had mortality rates as high as 80 percent. In 1979, dantrolene became the first drug approved by the FDA for the treatment of MH. According to the North American Malignant Hyperthermia Registry (NAMHR), mortality associated with MH is now less than 6 percent (Rosenberg et al., 2015). Although a life-saving drug, dantrolene is a highly lipophilic ryanodine receptor antagonist making it difficult to dissolve in water. It is commercially distributed in twelve 20 mg vials with twelve 60 ml vials of sterile water for reconstitution. In order to administer the recommended 2.5 mg/kg of dantrolene for a 70 kg patient, 175 mg of dantrolene must be dissolved in 525 ml of sterile water (Giraldo-Gutiérrez, 2018). Not only is reconstitution and administration of this drug time consuming in a very time sensitive situation, but the amount of fluid given to the patient is excessive. According to Cieniewicz et al., for every 30 minutes that treatment with dantrolene is delayed, the risk for complications doubles (2019).

Ryanodex, a dantrolene sodium nanosuspension, was introduced in 2014 as a more concentrated alternative to dantrolene. Supplied in 250 mg vials that require only 5 ml of sterile water for reconstitution, Ryanodex has gained much recognition as the new and improved treatment of MH (Just et al., 2015). While most surgery facilities that administer either volatile anesthetics or succinylcholine have a MH protocol in place, the decision regarding which dantrolene formulation to administer is often clinician preference. Ryanodex, with its safe and efficient properties, is more than double the price of dantrolene (Amar, 2016). Additional study is needed to determine true cost effectiveness of stocking Ryanodex in facilities that rarely treat MH patients. Moreover, the development of a decision making algorithm in facilities that stock both Ryanodex and dantrolene could reduce hospital spending while ensuring safe and effective patient care.

Review of Literature

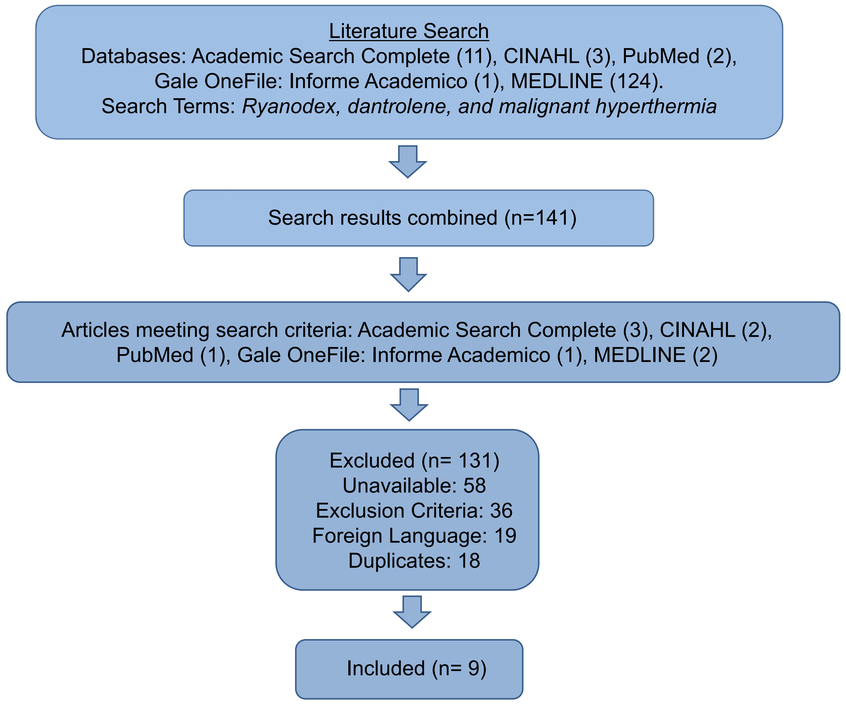

Table 1: Cost Comparison

Citation/Year	Drug (Trade Name)	Cost of Resources
Amar, 2016	a. Dantrium b. Revonto c. Ryanodex	a. $4,028 b. $3,192 c. $8,280
Denholm & Spruce, 2015	Dantrolen sodium vs Ryanodex	$196,320 per patient saved by stocking Dantrolene in ASF
Giraldo-Gutiérrez et al., 2018	a. Dantrium b. Ryanodex	a. $119.38 USD per vial b. $2,300.00 USD per vial
Khan, 2016	a. Dantrolene b. Ryanodex	a. $2,340 b. $6,900
Zavilla et al., 2016	a. Dantrolene (dantrium or revonto) b. Ryanodex	a. $62,000 annually to keep MH carts stocked with dantrolene b. “Ryanodex costs more than double”

References available upon request

Data Collection Process

A single investigator was involved in data collection from each article. While reviewing each article, the purpose and objective of this study was pertinent in determining inclusion or exclusion. Administration of either Ryanodex or dantrolene, patient outcomes, and costs of treatment with these medications were noted in order to perform a comparison of the two populations. Type of study, credibility of sources, and potential bias were reviewed to validate each study. Upon completing each article review, information was gathered that met the objective of examining current evidence and comparing the outcomes of malignant hyperthermia (MH) patients following administration of either Ryanodex or standard dantrolene.

Study Characteristics

Eight of the nine sources utilized in this study are journal articles. Within these articles, authors utilize continuing education tools and crossover studies. For each study, the additional following features were assessed: study size, drug used (either dantrolene or Ryanodex), limitations, independent and dependent variables, results, and implications for MH management. The resulting study characteristics with the categories listed above were then compiled in table format (see Table 1).

Conclusion

The introduction of dantrolene sodium in 1979 as the sole pharmacologic treatment for MH was positively revolutionary. In 2014, an improved version of this revolutionary drug was developed but its use comes at a much higher cost. Saving countless lives and improving patient outcomes, both dantrolene formularies are crucial to ensuring patient safety in the surgical population. While data is limited containing cost benefit analysis of the new drug Ryanodex, current literature supports the use of the drug prepared and administered with ease, thereby saving time and most importantly patients.

Nine articles met inclusion criteria and were utilized to perform a cost benefit analysis between traditional dantrolene and Ryanodex. Aside from increased cost and a shorter shelf life, Ryanodex ranks superior in all other categories. The potential risks to the patient of delayed treatment during MH crisis are great. Each study that compared initial dose preparation times was unanimous in reporting Ryanodex to be much easier and quicker to prepare and administer. Patients also benefited from receiving less volume and less mannitol with MH treatment. Finally, the highly concentrated vials of Ryanodex take up less space and are easier to transport in an emergency than the MH cart. Based on the results of this IRR, further data collection and research is needed to verify the long term benefits of utilizing Ryanodex over dantrolene in the treatment of MH.