Dantrolene and Malignant Hyperthermia Carts

Do We Need Them on Maternity Units?

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MALIGNANT hyperthermia. It is an anesthetic crisis that has been drilled into our heads since training. It is mostly unpredictable and rare—an individual anesthesiology provider may see it once in her/his lifetime or not at all. It is scary because of its rarity and because of its high fatality rate unless recognized early and treated appropriately. Fortunately, fatalities from malignant hyperthermia (MH) have fallen dramatically in the past three decades, primarily because of availability of dantrolene (which first became available in the United States in 1979) and the education of both anesthesia providers and operating room nurses. Education has been extensive; in the United States, education has been driven by the Malignant Hyperthermia Association of the United States (Sherburne, New York).

Founded in 1981 by families of patients who had died from MH and anesthesiologists, the Malignant Hyperthermia Association of the United States has developed and disseminated protocols for the treatment of an acute MH crisis. The protocols have included suggestions for contents of an MH cart, as well as a routinely updated, evidence-based protocol for the treatment of MH. Accrediting agencies, such as the Joint Commission, use the Malignant Hyperthermia Association of the United States recommendations to assess preparedness for an MH event during survey visits.

A fundamental aspect of successfully treating MH is the early administration of dantrolene. Because dantrolene is essential for the treatment of MH and the prevention of death and complications, the Malignant Hyperthermia Association of the United States has stated that “dantrolene must be available for all anesthetizing locations within 10 minutes of the decision to treat for MH.” This statement is based on consensus from the MH Hotline – Professional Advisory Council (May 14, 2011). Additionally, the organization does not recommend “sharing” a supply of dantrolene between anesthetizing locations. However, dantrolene is an expensive drug, and it often expires before use. Therefore, cost-conscious individuals and institutions have again raised the “sharing” question: what if the second anesthetizing location is on the same hospital campus, for example, a maternity unit that is within 10 min of the MH cart stored in the main operating suite? Does this adhere to the spirit of the Malignant Hyperthermia Association of the United States guidelines while minimizing cost? An article in this issue by Ho et al. addresses the cost-effectiveness of maintaining a fully stocked MH cart on the maternity unit compared to other less-expensive strategies, including stocking an initial dose of dantrolene on the unit with the plan to retrieve a centrally located MH cart during an MH crisis.

Ho et al. used decision-tree analysis to model the expected number of lives saved by having dantrolene immediately available on the unit (based on assumptions regarding the value of a statistical life) and the expected cost (based on assumptions regarding the incidence of MH events and the probability of death or complications with and without dantrolene, the cost of the dantrolene and other cart supplies, and the cost of maintaining the cart). Using these assumptions, and sensitivity analyses, the authors concluded that keeping a fully stocked MH cart on each maternity unit in the United States would reduce morbidity and mortality by $3.3 million but cost $5.9 million. The results are driven primarily by the low rate of general anesthesia on maternity units; the authors concluded that a cesarean delivery general anesthesia rate higher than 11% is required to make stocking the MH cart on the maternal unit cost-effective.

Instead, the authors proposed a cost-effective strategy—stocking an initial dose of dantrolene on the unit with the plan to administer this initial dose while retrieving the MH cart from a central location in the event of an MH crisis. The initial recommended dose of dantrolene is 2.5 mg/kg (total body weight). The Malignant Hyperthermia Association of the United States recommends stocking 36 vials (each vial contains...
20 mg; therefore, 36 vials is approximately 10 mg/kg for a 70-kg individual) in the MH cart. A new formulation of dantrolene, Ryanodex (Eagle Pharmaceuticals, USA), is formulated with 250 mg/vial; therefore, stocking three vials is recommended. Using a conservative weight estimation (100-kg individual), the initial dose of dantrolene is 13 vials (260 mg) of the older formulation and 1 vial of the newer formulation. Given that the newer formulation is more expensive, Ho et al. noted that the strategy of stocking the initial dose on the maternity unit is only cost-effective if the older, more dilute formulation is used.7

We could quibble about some of the assumptions used in building the authors’ model. For example, the value the authors used for estimating the incidence of MH is calculated from data from ambulatory surgery centers,8,9 where it is likely that most modern-day general anesthetics do not involve the use of succinylcholine (it is likely that almost all obstetric general anesthetics include a volatile agent and succinylcholine). Thus, this value may underestimate the incidence. We could quibble about the assumed general anesthesia rate for cesarean deliveries (5%); it is likely higher, at least in some institutions.10,11 However, I think the authors’ conclusions are likely correct. In general, they used conservative estimates (values that provide the highest reduction mortality if an MH cart is stored on the maternity unit) and confirmed their findings with multiple Monte Carlo simulations. Additionally, in reality, the general anesthetic rate necessary to achieve cost-effectiveness is probably higher than 11%. Approximately 60% of the deliveries in the United States are performed at centers with annual delivery rates less than 1,000.12 Inspection of the left side of the graph shown in figure 2 of the article by Ho et al.7 demonstrates that at the current cesarean delivery rate (32%), the break-even threshold for general anesthesia in an institution that has 1,000 deliveries per annum is approximately 15%.

I suggest, however, that Ho et al. did not consider several factors that may play an important role in the cost-effectiveness analysis, particularly their conclusion that the newer, concentrated formulation of dantrolene is not cost-effective.7 Their analysis did not take into account the cost of training nonanesthesia personnel (usually nurses) to reconstitute the older formulation dantrolene (20 mg/vial) with sterile water. This is not an easy task for someone who does not routinely reconstitute drugs13; it cannot be done by the anesthesia provider who is caring for the patient. In contrast, an anesthesia provider treating a patient with suspected MH can easily reconstitute the new formulation of dantrolene (250 mg in 5 ml water) and administer the drug without assistance from anyone else on the team (although assistance is still required for other tasks critical to successfully treating MH). The annual cost of training and retraining nursing staff to reconstitute the older formulation of dantrolene were not considered in the authors’ model.

Another important aspect of the authors’ calculation is the assumption that dantrolene and the other supplies and drugs necessary to treat an MH crisis can be delivered to the maternity unit in a timely manner when needed in a crisis. They concluded that the standards set by the Malignant Hyperthermia Association of the United States “can be fulfilled if a hospital demonstrates the ability to rapidly deliver an MH cart to the maternity unit within 30 min of a decision to treat [MH] and the maternity unit maintains an initial dantrolene treatment dose of 250 mg.”7 The 30-min threshold may be based on data from Larach et al.14; according to a multivariable model for predicting complications of MH, the likelihood of a complication increased 1.61 times (95% CI, 1.16 to 2.25) for every 30-min increase in time between the first sign of MH and the first dantrolene dose. However, in the middle of an MH crisis, I think the terms “rapidly” and “30 min” are contradictory. The median dose of dantrolene used to control an MH event is 5.9 mg/kg (1st and 3rd quartiles 3.0, 10.0).14 Thus, a majority of patients will need additional dantrolene beyond the initial dose. This second dose should be administered as soon as it is clear that the first dose is not suppressing the hypermetabolic reaction of the MH event. Response to dantrolene occurs within several minutes; thus, I usually recommend that the second dose of dantrolene be reconstituted during the interval in which clinicians are observing for the response to the first dose. This is especially important for the older dantrolene formulation because it takes many minutes to reconstitute. Thus, the second dose of dantrolene must be available to be reconstituted as the first dose is being administered. By my math (first dose of dantrolene at 10 min, second dose 10 min later), the second dose of dantrolene (and the accompanying MH cart) must be available on the maternity unit within 15 to 20 min of the decision to administer dantrolene (even in the middle of the night when a nurse or transporter from the maternity unit is dispatched to the empty main operating room suite to find the MH cart that is stored in the locked pharmacy or anesthesia workroom). It is not just a matter of knowing it takes 10 min to walk from point A to point B. The ability to reliably deliver the MH cart in a crisis requires education, including regular updates, and optimally, in situ simulations. These, too, cost money. This cost was not included in the authors’ analysis.

An additional complication of the authors’ proposal (storing 13 vials of the older formulation of dantrolene as a starter dose on the unit) is the storage of sterile water. The Malignant Hyperthermia Association of the United States recommends storing 100-ml vials of water in the MH cart to reconstitute the older formulation.5 Bags of sterile water are not recommended because they may be mistaken for intravenous fluid bags. Of note, similar to many other drugs, both 50- and 100-ml vials of sterile water are currently on shortage.15 The costs of managing drug shortages are not insignificant.

In summary, the exercise of calculating the cost benefit of specific therapies is critical to wise allocation of our limited resources. If we could afford it, we would make all proven life-saving therapies and strategies available to everyone everywhere, and we would save more lives. For example, we
could have level-one trauma centers in every hospital, or at least one in-house obstetric anesthesiologist in every hospital with a maternity unit. However, our healthcare system cannot afford this, and so we have to make decisions about where to invest our limited resources.

I agree with the authors’ conclusion that the strategy of stocking dantrolene and an MH cart in every anesthetizing location in which triggering anesthetic agents are administered, no matter the frequency of use of these drugs, should be reconsidered. The analysis, however, should not only take the rate of general anesthesia into account but should also consider training costs. It may indeed make more sense to annually train obstetric team members to obtain the MH cart from a central location. However, the details of how the dantrolene and other MH cart supplies will be transported to the maternity unit are critical to the decision making. A maternal (or any) death from MH attributable to the lack of timely availability of dantrolene is not justifiable in a United States hospital today.

Competing Interests
Dr. Wong is a Malignant Hyperthermia Association of the United States (Sherburne, New York) Malignant Hyperthermia Hotline Consultant. The views expressed in this editorial are solely those of the author and do not represent those of the Malignant Hyperthermia Association of the United States.

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