Estimate of the Relative Risk of Succinylcholine for Triggering Malignant Hyperthermia

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BACKGROUND: Facilities with volatile anesthetic agents stock dantrolene for the treatment of malignant hyperthermia (MH). The availability of dantrolene at these facilities satisfies cost-utility norms even for sites with as few as 1 anesthetic per workday, based on the overall incidence of MH per anesthetic. We considered the stocking of dantrolene at facilities with succinylcholine alone (i.e., where volatile anesthetics are not available), by using registry data and estimates of the frequency of administration of succinylcholine during anesthesia. We determine the magnitude of the relative risk of the administration of succinylcholine for triggering MH.

METHODS: The relative risk of triggering MH by succinylcholine versus volatile agents was calculated using data from 2 sources. The ratio of the number of cases of MH among patients receiving succinylcholine to number among patients not receiving succinylcholine was estimated from the previously published cohort of 284 cases of MH from the North American MH Registry of the MH Association of the United States (MHAUS). The percentage of anesthetics with succinylcholine was estimated using anesthesia information management system data from a typical North American hospital comprising tertiary operating rooms, obstetrics unit, ambulatory surgical center, and endoscopy and radiological suites.

RESULTS: The relative risk of MH with versus without succinylcholine was 19.6 (lower 95% confidence limit > 16.1). Limiting to cases with volatile anesthetics, the relative risk was 9.1 (>7.5). Both relative risks exceed 1.0 ($P < 0.0001$). Because more than half of the reported cases of MH included the use of succinylcholine, the relative risk exceeded 1.0 provided fewer than half of anesthetics in North America included the use of succinylcholine. The incidences of succinylcholine use at the hospital were 5.8% and 11.6% for all anesthetics and for anesthetics with volatile agents, respectively.

CONCLUSIONS: Our results provide no insight into the triggering mechanism for MH (i.e., succinylcholine could in isolation have an extremely low incidence of inducing MH, yet markedly increase the risk when administered in combination with volatile anesthetics). Until more epidemiologic data are collected and analyzed, having dantrolene available, where succinylcholine may be used, is reasonable, and this practice should be maintained. (Anesth Analg 2013;116:118–22)

Consensus guidelines recommend and some accreditation standards require that dantrolene be available at facilities where volatile agents or succinylcholine are present, because volatile agents and succinylcholine can[1] trigger malignant hyperthermia (MH).[2-3] In contrast, some organizations do not require dantrolene be stocked at facilities without volatile agents, unless succinylcholine is “used routinely,”[9] “part of the planned anesthetic,”[7] “used,”[4] or “administered.”[9] Some facilities performing only sedation, and having succinylcholine available only for emergency use, have questioned the need for dantrolene.[4] Ideally, we would have evidence-based recommendations for such facilities. In this study, we explore the relative risk of succinylcholine in triggering MH.

Dantrolene is available at facilities at which volatile anesthetics are used, even though a cost-utility study has not been performed.[2] Dantrolene is present not because MH occurs commonly, as the incidence of MH is very small (9.6 and 3.1 per million inpatient and outpatient 4Malignant Hyperthermia Association of the United States, accessed April 25, 2012 (http://medical.mhaus.org/index.cfm?Fuseaction=Content.Display/PagePK/MedicalFAQs.cfm) and American Association for Accreditation of Ambulatory Surgery Facilities, accessed June 2, 2012 (www.AAAASF.org/newsletters/ASF_Summer2008.pdf).
9On April 22, 2012, we performed a PubMed search for the following words in the title and/or abstract: cost AND dantrolene AND (utility OR effective ness). There was only 1 abstract (article), and it did not apply to MH.}
anesthetics, respectively). Rather, dantrolene is present because it reduces the mortality rate of MH from > 40% to 1.4%. Suppose that the relative risk of developing MH from the administration of succinylcholine was large. Then, by comparative reasoning, the established decision to have dantrolene available where volatile anesthetics are administered would apply also to facilities where succinylcholine is used without volatile agents. Therefore, we used registry data and estimates of the frequency of administration of succinylcholine during anesthetics to determine the magnitude of the relative risk of the administration of succinylcholine for triggering MH.

**METHODS**

The Thomas Jefferson University IRB approved this retrospective study without a requirement for informed consent. The following calculations were made to estimate the relative risk of MH from succinylcholine administration. Let \( N_x \) refer to the number of cases with the characteristic \( x \), “Sux” refers to succinylcholine, MH to malignant hyperthermia, and \( p_x \) to the proportion of cases with the characteristic \( x \). Then,

\[
\begin{align*}
\text{Succinylcholine Administered} & \quad \text{Yes} & \quad \text{No} \\
\text{Positive} & \quad N_{\text{SuxMH}} & \quad N_{\text{Sux}} \\
\text{Negative} & \quad N_{\text{NotSuxMH}} & \quad N_{\text{NotSux}}
\end{align*}
\]

\[
P_{\text{Sux}} = \frac{N_{\text{Sux}}}{N_{\text{SuxMH}} + N_{\text{NotSuxMH}}} \quad \text{Relative risk} = \frac{N_{\text{SuxMH}}/N_{\text{Sux}}}{(N_{\text{NotSuxMH}}/N_{\text{NotSux}})} + (N_{\text{SuxMH}}/N_{\text{NotSuxMH}}) \left( \frac{N_{\text{NotSux}}}{N_{\text{Sux}}} \right) + (N_{\text{SuxMH}}/N_{\text{Sux}}) - 1 \quad \text{(1)}
\]

The first term \( N_{\text{SuxMH}}/N_{\text{NotSuxMH}} \) was estimated from Table 1 of the previously published cohort of 284 cases of MH from the North American Malignant Hyperthermia Registry of the Malignant Hyperthermia Association of the United States (MHAUS). These data are from all of the United States and Canada.

The second term \( (1/P_{\text{Sux}}) - 1 \) was estimated using anesthesia information management system (AIMS) data from Thomas Jefferson University Hospital, a typical North American facility, which comprised of tertiary operating rooms, obstetric unit, ambulatory surgical center, and endoscopy and radiological suites. There is an active electroconvulsive therapy service, Level 1 trauma service, and obstetrical, general, and orthopedic surgery services. Care is provided by resident physicians and certified registered nurse anesthetists. Sugammadex is unavailable as for other US hospitals. The AIMS captures >98% of anesthetics in the hospital. Data were extracted from the AIMS database (Innovian® Dräger, Telford, PA) for all anesthetics administered between October 18, 2005 (the AIMS implementation date) and July 5, 2011 (final date in the dataset when the analysis was performed). Analyses were repeated limiting consideration to patients receiving volatile anesthetics.

The 95% lower confidence limits for the relative risks were calculated using exact methods (StatXact-9, Cytel Software Corporation, Cambridge, MA). The \( P \) values were also calculated using exact methods, but since small were reported as \( P < 0.0001 \).

**RESULTS**

Using all cases in the MH registry and all AIMS anesthetics at Thomas Jefferson University Hospital, the relative risk of MH with versus without succinylcholine was 19.6, where

\[
19.6 = \left( \frac{155 \text{ with succinylcholine}}{129 \text{ without succinylcholine}} \right) \times \left( \frac{235,992 \text{ cases}}{13,618 \text{ with succinylcholine}} - 1 \right)
\]

The lower 95% confidence limit was 16.1.

Using cases with volatile anesthetics in the MH registry and at Thomas Jefferson University Hospital, the relative risk of MH with versus without succinylcholine was 9.1, where

\[
9.1 = \left( \frac{153 \text{ with succinylcholine}}{128 \text{ without succinylcholine}} \right) \times \left( \frac{100,745 \text{ cases}}{11,674 \text{ with succinylcholine}} - 1 \right)
\]

The lower 95% confidence limit was 7.5. An implication of this result is that reduced use of succinylcholine will reduce the incidence of MH.

Using cases with volatile anesthetics, the calculations can be performed, but the confidence limit is (of course) much wider because the numerators are small. The relative risk of MH with versus without succinylcholine was 137, where

\[
137 = \left( \frac{12 \text{ with succinylcholine}}{1 \text{ without succinylcholine}} \right) \times \left( \frac{135,247 \text{ cases}}{1944 \text{ with succinylcholine}} - 1 \right)
\]

The lower 95% confidence limit was 18. The calculated risk is larger than the other 2 because, among patients not receiving volatile anesthetic, the incidence of use of succinylcholine was less (1.4%).

The 3 relative risks exceed 1.0 \((P < 0.0001)\). To investigate the sensitivity of the results to the percentage of anesthetics with succinylcholine, consider that at least half the cases of MH included the use of succinylcholine: 55% \((N = 155 / 155 + 129, 95\% \text{ lower confidence limit } 50\%)\). Consequently, the first term in equation (1), \( N_{\text{SuxMH}} / N_{\text{NotSuxMH}} \geq 1\). The relative risk exceeds 1.0 provided the second term \( (1/P_{\text{Sux}}) - 1 > 1\). Rearranging the terms, the relative risk remains much greater than 1.0, provided fewer than half of the anesthetics in North America included the use of succinylcholine (i.e., \( P_{\text{Sux}} < 50\% \)). From the Thomas Jefferson University Hospital

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9 The established decision is reasonable, based on cost utility. From contingent valuation studies, a life is reasonably worth $3 million. Multiplying by (3.1 per 1 million anesthetics) × 40% mortality gives $3.72 per anesthetic.

10 Stocking 36 vials of dantrolene with a shelf life of 36 months averages 1 vial per month. Using 255 workdays per year and $80 per vial for dantrolene, stocking dantrolene is breakeven from a societal perspective, provided a facility averages at least 1 anesthetic per workday, where 1 = $80 ÷ ($3.72 × 255/12).
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...data, the \( p_{\text{sux}} = 5.8\% \) in equation (2) and \( p_{\text{sux}} = 11.6\% \) in equation (3). Thus, the result that the relative risks exceed 1.0 is (highly) insensitive to the proportion of cases in which succinylcholine was used (e.g., unaffected by the decreasing incidence of use of succinylcholine over the past decade).

**DISCUSSION**

One of the stated primary goals of MHAUS is to “advise and prepare all medical facilities in the United States for prompt diagnosis and immediate treatment of an MH episode.”11 Most (>50%) cases of MH in North America have included succinylcholine.11 Thus, our results show that this primary goal of MHAUS cannot be satisfied unless facilities stocking succinylcholine also stock dantrolene.

The quantitative results of relative risks >7.5 do not advance the understanding of the triggering mechanism for MH. There are multiple case reports of MH being caused by succinylcholine alone without volatile anesthetics.11,12 However, almost all MH patients in the registry receiving succinylcholine also received a volatile anesthetic. Thus, the relative risks that we estimated are principally that of MH during volatile anesthesia with versus without the use of succinylcholine. Succinylcholine may have, in isolation, an extremely low incidence of inducing MH, yet markedly increase the risk when administered in combination with volatile anesthetics.

The calculated large relative risks of MH during anesthetics including succinylcholine versus without the drug may help health systems with policy decision making regarding the stocking of dantrolene. Consider a health system that has the recommended 36 vials of dantrolene immediately available at all facilities at which volatile anesthetics are administered (footnote a in the Introduction).2 No cost-utility assessment has been published (see footnote f in the Introduction). Consequently, the health system’s decision cannot have been based on a published cost-utility analysis, regardless of the fact that the footnote \( h \) in the Introduction shows that the cost utility is strongly in favor of stocking dantrolene. Because the health system’s decision to stock dantrolene for volatile anesthetics was not based on cost utility, by analogy, the health system should not base the succinylcholine–dantrolene decision on cost utility, either. Because at least half the cases of MH have been triggered during anesthetics where succinylcholine was administered, despite the fact that this drug is used infrequently (e.g., 5%–10% of anesthetics), the consistent decision would be to have dantrolene immediately available in all locations where succinylcholine might be used, including those where volatile anesthetics are not available. This would hold regardless of the motivations for stocking dantrolene where volatile anesthetics are administered (e.g., clinical responsibility or concern about legal liability).

Health systems may instead want an evidence-based cost-utility analysis for the stocking of dantrolene at facilities at which the only triggering agent is succinylcholine, and the use of succinylcholine is reserved for emergency airway management (e.g., as discussed in footnote \( h \) in the Introduction). The health system should then mandate that all its facilities report the following 3 data to the same 1 publically reporting registry to which the facilities of other health systems report, because local data will be insufficient, given the very low incidence of MH (see footnote \( g \) in the Introduction).

First, the incidence of MH at facilities without volatile anesthetics needs to be known.13 During the past 19 years, the MH registry had 286 episodes of MH recorded. More than 20 times as many cases may have occurred based on inpatient and outpatient survey data. All suspected cases of MH, including those for which dantrolene is used regardless of whether succinylcholine was used, should be reported to 1 publically reporting central registry. Approximately 0.5% of patients with a personal or family history of MH were reported to have developed MH during the administration of anesthetics that avoided known triggering agents for muscle biopsy.7,14,15 Among 248 MH cases in the North American registry, 1 child with a positive family history of MH developed signs of MH after the administration of a propofol anesthetic in the absence of succinylcholine.11,16 It is essential to know the actual perioperative incidence of MH without succinylcholine to decide whether to stock dantrolene at sites not administering triggering agents other than for emergency use.

Second, the incidence of emergency use of succinylcholine needs to be known among facilities performing only moderate or deep sedation (i.e., no anesthesia machines with vaporizers are present). Anesthesiologists’ judgments about the incidence of adverse events from succinylcholine are known to be inaccurate.9,17,18 Thus, opinion surveys are unreliable. Even though succinylcholine may be available at ambulatory facilities for emergency tracheal intubation,17 a PubMed search did not reveal any article describing the use of succinylcholine for this intervention during deep sedation.19,20 The unplanned use of succinylcholine could become a mandatory reported item for registries.

Third, the incidences of laryngospasm, treatments (including the use of succinylcholine), and outcomes need to be known. Among a large case series of children undergoing deep sedation, laryngospasm incidences are 0.3% by pediatric critical care physicians,20 0.2% by pediatric emergency medicine physicians,21 and 0.2% by pediatric anesthesiologists.22 Among pediatric anesthesiologists, 15% (3/20) of patients received succinylcholine for the treatment of laryngospasm after positive pressure (7/20 patients) and extra propofol (10/20) were insufficient.23 The product of the 2 incidences gives the probability of both events occurring together. The value of 0.03% is close to the incidence of such treatment of laryngospasm among pediatric dental anesthetics.3 However,

\[1 \text{http://www.mhaus.org/about-mhaus, accessed June 2, 2012.}\]

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the incidences are unknown for other providers of moderate or deep sedation and for adult patients. Knowing these latter incidences is important because they account for more than one third of ambulatory anesthetics nationwide. \textsuperscript{12,14,25,16} Monitored anesthesia care accounts for 50% of closed claims for anesthesia in nonoperating room locations, and respiratory depression is the most common cause. \textsuperscript{16,27}

In conclusion, at least half the cases of MH in North America have included succinylcholine, even though succinylcholine was present for a much smaller percentage of anesthetics (e.g., 5\%-10\% of cases). Until more epidemiologic data are collected and analyzed, the consensus guidelines\textsuperscript{2,3} to have dantrolene available where succinylcholine is present are reasonable, and this practice should be maintained.

DISCLOSURES

Name: Franklin Dexter, MD, PhD.

Contribution: This author helped design the study, conduct the study, analyze the data, and prepare the manuscript.

Attestation: Franklin Dexter approved the final manuscript. This author attests to the analysis reported in this manuscript.

Name: Richard H. Epstein, MD, CPHIMS.

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RECUSE NOTE

Dr. Franklin Dexter is the Statistical Editor and Section Editor for Economics, Education, and Policy for the Journal. This manuscript was handled by Dr. Sorin J. Brull, Section Editor for Patient Safety, and Dr. Dexter was not involved in any way with the editorial process or decision.

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\textsuperscript{1}Nancy Setzer, MD, and her colleagues of Pediatric Dental Anesthesia Associates reported in 2009 a case series of 7581 anesthetics in which they administered muscle relaxants for laryngospasm in 5 patients (0.06\%, personal communication, Hector Vila, Jr., April 24, 2012).

\textsuperscript{2}Alternatively, (very) large comparative outcome studies could evaluate if facilities need to have succinylcholine. A Japanese teaching hospital that chose not to have succinylcholine reported 85,708 consecutive anesthetics with 4 intraoperative cardiac arrests and 1 death, all unrelated to failed intubation or laryngospasm. \textsuperscript{21}

REFERENCES