

Succinylcholine and Dantrolene

Inseparable in the Emergency Cupboard?

Philip M. Hopkins, M.B., B.S., M.D., F.R.C.A.

In this issue, Larach *et al.*¹ conclude a large database analysis and systematic review by advocating that dantrolene be stocked in all locations where succinylcholine is available, even if volatile anesthetics are not. The premise for the analysis is that if succinylcholine is used in such locations (e.g., for airway rescue or routinely for electroconvulsive therapy), and succinylcholine without volatile anesthetics can trigger a malignant hyperthermia (MH) reaction that requires dantrolene to be immediately available, then dantrolene should be stocked at these locations. The authors did not conduct a health economic analysis of the cost benefit of stocking dantrolene in this context, instead referring to a previous health economic analysis of the wider question of whether it is cost-effective to stock dantrolene in ambulatory surgery centers where any MH-triggering drug is likely to be available.²

The context of the study is conflicting recommendations from the Malignant Hyperthermia Association of the United States, which advocates availability of dantrolene,³ and from the Society for Ambulatory Anesthesia, which suggests availability of dantrolene is not mandatory.⁴ In attempting to address the issues at stake, Larach *et al.*¹ have completed a gargantuan task. They have interrogated three large databases and undertaken systematic reviews of the literature. In designing their study, the authors encountered several problems common to database studies. For example, the Multicenter Perioperative Outcomes Group database does not explicitly record the use of succinylcholine for airway rescue, and so a surrogate outcome was used. Throughout their manuscript, the authors enable the reader to appreciate the limitations of the study. Nonetheless, it seems reasonable



“[Increased] patient safety is served by mandating that dantrolene be stocked where succinylcholine is available.”

for the authors to conclude that succinylcholine is used on a regular basis for airway rescue in the hospital setting. There is also evidence to support the conclusion that delay in the administration of dantrolene is associated with poorer outcomes in MH, although these data are not restricted to cases where succinylcholine was the sole trigger of the MH reaction.

If one assumed that the nature of a MH reaction is the same whether triggered by volatile anesthetics alone, succinylcholine alone, or a combination of volatile anesthetics with succinylcholine, then it would be reasonable to extrapolate the data concerning delay in dantrolene and MH outcomes from all MH events to those triggered by succinylcholine alone. However, this is not the case either in human MH or the porcine model.⁵ The response to succinylcholine in MH-susceptible individuals is characterized by muscle rigidity and rhabdomyolysis. Other than these features, normal pharmacologic and physiologic responses to succinylcholine may confuse the situation. For example, succinylcholine causes a dose-dependent increase in heart rate in adults.^{6,7} If the patient develops muscle rigidity, the muscular activity generates heat (as with a generalized seizure), whereas a delay in securing the airway may be associated with inadequate elimination of carbon dioxide and hypercarbia. Only a careful evaluation of the contemporaneous anesthesia record is likely to distinguish between these consequences of succinylcholine in a MH-susceptible individual and the development of a progressive hypermetabolic response that is the *sine qua non* of a MH reaction. Indeed, 30 yr of evaluating suspected MH reactions has taught me that attempting to evaluate the likelihood of MH from case vignettes is wholly inadequate because of the crucial importance of the temporal

Image: J. P. Rathmell.

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relationships in the evolution of the clinical features of MH appraised in the context of surgical and anesthesiologic interventions. Similarly, without the contemporaneous anesthesiology records, it is not possible to verify an MH clinical grading score because of the assumptions required before allocating a score in several of the categories.⁸

The other criterion used by Larach *et al.*¹ to support the recognition of cases of MH triggered by succinylcholine alone was the determination by MH experts that administration of dantrolene was indicated. It is a shame that the article does not specify what criteria were used to indicate a requirement for dantrolene. Again, I would have to admit that I would not feel capable of judging whether dantrolene was required without recourse to the contemporaneous records.

Although the evidence presented in this article is insufficient to convince me that succinylcholine in the absence of volatile anesthetics can trigger a life-threatening progressive hypermetabolic response in MH-susceptible patients, the evidence is similarly insufficient to rule out that this is the case. My view, therefore, is that equipoise is retained on this issue, and while it remains, patient safety is served by mandating that dantrolene be stocked where succinylcholine is available.

Further health economic analysis, although perceived as unnecessary by Larach *et al.*,¹ may be seen by some as the answer to this conundrum. Even taking the worst case scenario that could be extrapolated from the data accumulated by Larach *et al.*¹ in situations where succinylcholine is used routinely, such as for electroconvulsive therapy, the requirement for dantrolene would be extremely rare. The cost of stocking dantrolene in relevant locations (on a cost per case basis) will depend on the total case throughput of the facility. For example, any facility treating more than 1,200 cases a year would be required to spend less than an extra \$1 per case to maintain a supply of 720 mg of the traditional formulation of dantrolene (this rises to a caseload of 3,500 patients a year with the new lyophilized formulation of dantrolene). How this information is translated into a value judgement may then depend on the healthcare funding system in place. For example, where the marginal cost of maintaining a stock of dantrolene can be passed on to the patient either directly if they self-pay or indirectly if they have health insurance and then viewed as a marginal cost per patient, dantrolene may be perceived to be good value. However, in a nationalized healthcare system paid from general taxation, as in the United Kingdom, where there is a finite total healthcare budget, cost-effectiveness is viewed from a population perspective and weighed against other potential uses for the money. Having said this, where general anesthesia can be administered in the United Kingdom is more tightly regulated than in the United States, such that the only isolated anesthesia-providing locations where succinylcholine, but not volatile anesthetics, is used are largely confined to those sites where electroconvulsive therapy is given. Based on a rough estimate of the number of electroconvulsive therapy-providing locations and the total number of patients

receiving electroconvulsive therapy in England,⁹ maintenance of a supply of dantrolene adds approximately \$20 to the electroconvulsive therapy treatment of each patient.

In conclusion, from a patient safety perspective, it is appropriate to recommend that dantrolene is stocked at all locations where succinylcholine is available. The cost per patient will depend on the size of the facility, whereas the value judgements that underpin decision-making are likely to depend on the relevant healthcare funding system and who makes that judgement.

Competing Interests

Dr. Hopkins is the Chair of The European Malignant Hyperthermia Group.

Correspondence

Address correspondence to Dr. Hopkins: p.m.hopkins@leeds.ac.uk

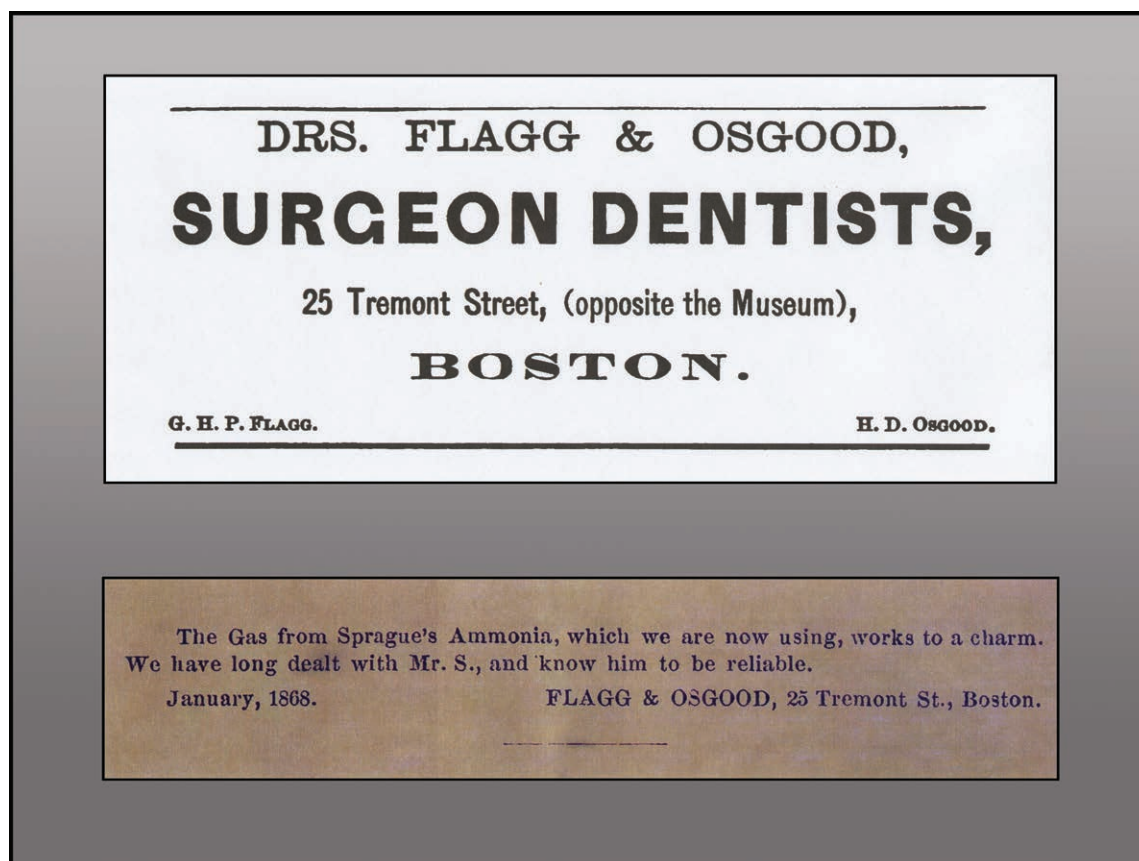
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The Patent Trail from Etherist W. T. G. Morton to Laughing-Gas Pioneer G. Q. Colton



In 1849 by marrying Elizabeth, sister of ether patentee W.T. G. Morton, G. H. P. Flagg clinched a job the following year as his brother-in-law Morton's dental assistant. By 1861, still on Tremont Street some seven years after having left Morton's office, Flagg had become senior partner of the Boston dental firm of "Flagg & Osgood" (*upper advertisement*). In 1864 his junior partner's brother, James, patented the thermoregulating nitrous-oxide generators modified by A. W. Sprague for G. Q. Colton's use throughout the United States and over in Europe. As implied by his 1868 testimonial for Sprague's ammonium nitrate ("Ammonia," *lower advertisement*), Flagg had shifted from etherizing patients alongside Morton to "laughing-gassing" patients alongside the Dentist(s) Osgood. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

George S. Bause, M.D., M.P.H., Honorary Curator and Laureate of the History of Anesthesia, Wood Library-Museum of Anesthesiology, Schaumburg, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.