**Supplemental Digital File 9. Question 3b, (Query 8): What is the impact of dantrolene administration on malignant hyperthermia (MH) mortality in the US and Canada? Does the time of dantrolene or initial dosage affect the likelihood of MH mortality in the US and Canada?**

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**Summary:** A total of 5 references (all Oxford Centre for Evidence-based Medicine level 3 or 4) were identified with the prospective Kolb *et al.* study (reference 1) demonstrating that timely administration of dantrolene (no more than 6 hours after the initial MH sign) decreased mortality from 75% to 0%. This was a highly significant result in a small, unblinded prospective study that provided the evidence for FDA approval for the use of intravenous (**iv**) dantrolene to treat MH. Subsequent retrospective North American Malignant Hyperthermia Registry of the Malignant Hyperthermia Association of the United States (**NAMHR**) studies for the reporting period of 1987 through 2012 showed that initial dantrolene (mg/kg) doses did not differ between those who died of MH and those who did not. The time intervals between 1st sign of MH and the 1st dantrolene administration also did not differ between these two groups. Because of the low number of reported patient deaths in reference #5, the power to detect a difference in the timing of the administration of dantrolene was very low (only 18%). However, in an initial NAMHR study with only 4 deaths, the total dantrolene dose (mg/kg) was higher in those who died of MH when compared to those who did not. The NAMHR studies may have been limited by possible selection bias, reporting, and recall bias. Further, those who experienced an MH death were not able to undergo MH diagnostic muscle biopsies*.*  However, for reference # 5, of the 8 patients who died, 6 were genotyped and 4/6 were confirmed to have had MH causative RYR1 mutations. 2/6 had RYR1 variants of unknown significance.

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| Article Identifier | Mortality  | Dantrolene | Classification of MH Event | Levelof Evidence | Bias | Other Comments |
| 1. Kolb ME, Horne ML, Martz R. Dantrolene in human malignant hyperthermia. Anesthesiology1982; 56:254-62
 | Death or survival were endpoints; Table 1 lists equivocal MH cases; Table 2 lists probable MH cases; One patient in probable MH appears to be equivocal but not sure when dantrolene given; this patient died. Mortality with delayed (>24 h) administration of dantrolene 75%; n=4Timely administration of dantrolene – (under ?6 hours) 100% survival n=11 | First early study to show value of dantrolene in human MH. Patients that got dantrolene late – 75% died; all patients that got dantrolene soon after diagnosis survived. No structured dantrolene dosing protocol but most used 1 mg/kg and then authors provided a mean starting dose givenBasis for 2.5 mg/kg as starting dose in humans. In 11 patients with unequivocal or probable MH, the mean dose of dantrolene was 2.5±0.5 mg/kg | MH event was diagnosed clinically, ABGs, and when possible muscle biopsy and by review by anesthesiology experts in MH; in some cases, muscle biopsy confirmed MH.  | 4Direct human evidence – level is high  | Patients with cardiac arrest or delay of more than 6 hours before treatment were excluded from statistical analysis; unblinded with multiple anesthesiologists adhering to standardized protocol and case report form | Diagnosis was by clinician experts in MH; no definite protocol of dantrolene administration; authors calculated average dose of dantrolene used (formed basis of suggested starting human dose); one patient included as probable MH appears to have had MH – dantrolene was given but not sure when it was given; patient did not survive. Unlikely that this data series has an overlap. MH susceptible patients who were biopsy positive did not get triggering agents but did get dantrolene despite no triggering agents and signs suggestive of MH. Dantrolene appeared to reverse some of the symptoms. Patients were from US and Canada with 65 institutions participating in study over 18 months although only 21 patients with apparent MH were treated with iv dantrolene by 16 anesthesiologists. 95% power to detect a difference of 0.025 level beween a dantrolene survival rate of 85% and the projected survival rate of 50%.This study led to FDA approval of iv dantrolene. |
| 2. Larach MG, Brandom BW, Allen GC, Gronert GA, Lehman EB. Cardiac arrests and deaths associated with malignant hyperthermia in North America from 1987 to 2006: a report from the North American Malignant Hyperthermia Registry of the Malignant Hyperthermia Association of the United States. Anesthesiology 2008;108:603-11 | Relative to the cases without cardiac arrest or death, those who arrested were 49.7 times more likely to develop DIC\*\*. The odds ratio of dying was 49.7 (6.9-596.5) P=0.000 if the patient experienced DIC. (The authors quote a Danish study as follows:The Danish Register analyzed all cases between January 1, 1978, and July 1, 1984, when dantrolene had just been introduced, with 10% mortality in 10 fulminant cases7 vs. 179) | The authors did not indicate the impact of dantrolene dose on DIC. Analysis only looks at the total dantrolene dose being significantly different between those with cardiac arrest and/or death and those without. (10.1 vs 5.0 mg/kg) Also, total dantrolene dose for fatal vs nonfatal MH was significantly different (11.1 vs 5.1 mg.kg) Personal communication from M. G. Larach on 7.31.17: Initial dantrolene dose was not significantly different between those who died and those who did not nor was there a significant difference between time of 1st MH sign and time of initial dantrolene dose. This data is found in the methods and results section of paper e.g. if not listed as significant, it was not significantly different and did not appear in Table 3. See also discussion section: “There were no reported differences in outcome (cardiac arrest/death implied) as regards time to MH diagnosis or treatment.”. [Nothing in table on timing of dantrolene dose or amount of initial dantrolene dose.]Dantrolene was used in 91.9% of patients, with a mortality rate of 1.4% | CGS\* score of >=35 =Rank 5 and 6 or “very likely” or “almost certain” MH-no genotyping or contracture confirmation of MH susceptibility | 3 | NAMHR data for AMRAs received from 1/1/1987\* through 12/31/2006 Reporting and recall bias; selection bias Not classic case control study and confounding is present;“associations do not imply causation”\*Earliest AMRAs did not include complication question. | Majority of patients from the US |
| 3. Larach MG, Gronert GA, Allen GC, Brandom BW, Lehman EB. Clinical presentation, treatment, and complications of malignant hyperthermia in North America from 1987 to 2006. Anesth Analg 2010;110:498-507 | No data on dantrolene and MH mortality22 patients of 229 patients received no dantrolene and survived their event without cardiac arrest. 2 of the 11 for whom information on complications were available had a complication. Those treated with dantrolene were 2.97 times more likely to have an “almost certain” episode than those not treated with dantrolene.  | Regardless of outcome, clinicians treated 229 MH patients with a median initial dantrolene dose of 2.4 (1st quartile 1.9, 3rd quartile 2.8) range 0.01-15.0 mg/kg and a total dantrolene dosage for 229 MH events was a median of 5.9 (1st quartile 3.0, 3rd quartile 10.0) range 0.02-100.00 mg/kg.  | CGS score of >=35 =Rank 5 and 6 or “very likely” or “almost certain” MH-no genotyping or contracture confirmation of MH susceptibility | 3 | NAMHR data for AMRAs received from 1/1/1987§ through 12/31/2006 Reporting and recall bias; selection bias Not classic case control study and confounding is present;“associations do not imply causation”§Earliest AMRAs did not include complication question. | Reference 2 and 3 patients are from the same dataset and completely overlap. Majority of patients from the US. |
| 4. Nelson P, Litman RS. Malignant hyperthermia in children: An analysis of the North American Malignant Hyperthermia Registry. Anesth Analg 2014; 118:369-74 | Dataset includes patients up to and including 18 years of age. Deaths occurred between 1990 and 2010. 10/264 (3.8%) died with no deaths in the 0-24 months age group. | Overall 188/254 (74%) of surviving patients received dantrolene but only 5/10 (50%) of those who died had received dantrolene. Of the 5 who received dantrolene, 2 died during a recrudescence (4-year old recrudesced 6 hours after the initial event and a 14 year old recrudesced 24 hours after the initial event). No data on dantrolene doses of those who died. No data presented on time of 1st dose of dantrolene in anyone in this dataset. | CGS score of >=35 =Rank 5 and 6 or “very likely” or “almost certain” MH-no genotyping or contracture confirmation of MH susceptibility | 3 | NAMHR of MHAUS data fro AMRAs with events reported between 1960 to 2011. Reporting and recall bias; selection bias Not classic case control study and confounding is present;“associations do not imply causation” | Unclear overlap between references 2, 3, and 5.  |
| 5. Larach MG, Brandom BW, Allen GC, Gronert GA, Lehman EV: Malignant hyperthermia deaths related to inadequate temperature monitoring, 2007-2012: a report from the North American Malignant Hyperthermia Registry of the Malignant Hyperthermia Association of the United States. Anesth Analg 2014; 119:1359-66 (Other: NAMHR of MHAUS dataset)  | Did not discuss dantrolene and its use and relationship to mortality.(Longer anesthetic exposures before dantrolene were associated with higher peak temperatures.) | Not published but drawn from the same dataset-see below. There was no significant difference in the initial dose of dantrolene/kg given to those who died and those who survived. Median of 2.47 mg/kg for those who survived vs. 2.22 mg/kg. for those who died. There was no significant difference between the time of 1st MH clinical sign and initial dantrolene dose. Median of 30 minutes for survivors vs. 66 minutes for those who died (missing information for 3 of the 8 who died). However, the power to detect a difference in the timing of the administration of dantrolene was very low (only 18%). Personal communication from M. Larach on 7/31/17. Analysis found in cardiac arrest 2010-2113comparisons.pdf in dantrolene review files of MGL on p. 30 and 36 of the files. Power calculations from email from E. Lehman to M Larach on 10/9.13.*Raw data available to do this analysis in published excel supplement file (070714PMsupplement-2.xlsx}.* Total dose of dantrolene for 59 MH patients irrespective of outcome (25 with missing data) was median of 7.0 mg/kg (467 mg) with a lower quartile of 3.0 mg/kg (180 mg) and an upper quartile of 10.0 mg/kg (810 mg), range 1.01 mg/kg (48 mg) to 16.71 mg/kg (1,700 mg). Personal communication from Marilyn Green Larach, M.D., F.A.A.P. on 2/23/18 based on data from cardiacarrest2datasetsummary-22.pdf. | ‘very likely’ or ‘almost certain’ MH event. For 6 of the 8 MH deaths, geneotyping was performed with 4 MH-casuative RYR1 mutations and 2 RYR1 variants of uncertain significance. (The Arg2508His mutation is now recognized to be MH causative. #30 on the EMHG¶ list.) | Not applicable | NAMHR data for AMRAs received from 1/1/2007 through 12/31/2012 Reporting and recall bias; selection bias Not classic case control study and confounding is present;“associations do not imply causation” | Not published as part of a paper. Dataset for Anesth Analg 2014; 119:1359-66) Personal communication from Marilyn Green Larach M.D., F.A.A.P. on June 12, 2016. Based on reporting of individual completing AMRA. Usually no hospital charts available to review. |
| **Summary**References 1. Establishes role of dantrolene in treating MH. Some evidence that sooner administration better.
 | Relevant references that meet protocol=5Only a few of the references above discuss dantrolene and mortality directly; the first reference is the best in that regard; as discussed in this first paper, same is found in other references detailing delay in starting dantrolene and increased mortality.  | Re: reference #5 For small dataset from the Registry (n=84 patients) However, the power to detect a difference was only 18% T**here was no significant difference in the initial dose of dantrolene/kg given to those who died and those who survived. Median of 2.47 mg/kg for those who survived vs. 2.22 g/kg. for those who died. Nor was there a significant difference between the time of the 1st MH clinical sign and the initial dantrolene dose. Median of 30 minutes for survivors vs. 66 minutes for those who died (missing information of 3 of the 8 who died). For earlier NAMHR dataset, the total dantrolene dose for 229 MH patients (reported to the NAMHR between 1987 through 2006) regardless of outcome was a median of 6 (1st quartile 3,3rd quartile 10) mg/kg.** | Classification of MH EventRef Larach (2010)D5-D6Ref Larach (2014)D5-D6 | Level of Evidence3 | BiasIncomplete data possible,No classic case control studiesReporting and recall bias; selection bias confounding, associations do not imply causality | CommentsReferences Larach (2004, 2007) primarily US cases.The above references are after a complete review of all references on PubMed, Cochrane data and Medline searches.  |

\*CGS=Clinical Grading Scale

\*\*DIC=disseminated intravascular coagulation

¶EMHG=European Malignant Hyperthermia Group