Malignant Hyperthermia: The Minnesota Connection

by John Capacchione, Tae Kim, David Beebe, James Mickelson, Paul Iaizzo, Kumar Belani

On September 23 and 24, the University of Minnesota will host the 2017 MHAUS Scientific Conference at the McNamara Alumni Center in Minneapolis. This conference is entitled “Malignant Hyperthermia: Risks and Associated Muscle Disorders.” (Visit the MHAUS website www.mhaus.org for more details about the conference and to register).

While Minneapolis may be a geographically convenient, centrally located hub for all North American attendees, the significance of this location should not go unnoticed, as Minnesota is also a historic North American hub for malignant hyperthermia (MH) testing and research. In fact, three of the five North American MH Testing Centers have personal connections with Minnesota. The following brief history is intended to reflect Minnesota’s contribution to MH, and to commemorate the 21 years since the last MHAUS Scientific Conference was held in Minneapolis; it is in no way meant to be all-inclusive, nor is it intended to minimize the contributions made by those from other regions of the world.

In 1987, when MHAUS began to hold a series of conferences to discuss the development of a standardized protocol for skeletal muscle contracture testing using caffeine and halothane (CHCT), there were 17 participating U.S. and Canadian MH diagnostic centers. Five of those centers were represented in the Midwest. Today, only the University of Minnesota (UMN) Medical School remains a Midwest MH testing site.

Although the UMN was not yet an MH testing location in 1987, its future Muscle Biopsy Center Director, Paul Iaizzo, Ph.D., did participate in the CHCT validation process as a Mayo Clinic faculty member. Dr. Iaizzo performed the first CHCT at the UMN on February 24, 1992, for a patient on whom Kumar Belani, M.D. performed the clinical evaluation. Around that same time, genetic testing for MH began to emerge, but it took almost two decades before both the CHCT and genetic screening were offered at the same Midwest location. Through Dr. Belani’s efforts, the UMN MH Testing Center partnered with the university’s Molecular Diagnostic Laboratory in 2012 so that MH genetic testing could be performed under the same roof. Thus, it became the first U.S. testing site to provide both the diagnostic CHCT and genetic testing in a CLIA (Clinical Laboratory Improvement Amendments) accredited laboratory.

The origins of Minnesota’s connection with MH testing and research began 75 miles south of Minneapolis at the Mayo Clinic in Rochester. It was here in the 1970’s that Gerald Gronert, M.D. became interested in MH while researching succinylcholine-induced hyperkalemia in a swine burn model. When one of Dr. Gronert’s research swine serendipitously triggered with an

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Circulating Knowledge: the basic premise that compels many of those involved within the MHAUS organization and its members. We are driven to share information that can save lives! We don’t want to hold onto it and keep it safe within the confines of the inner hierarchy; rather we strive to spread it out as far from our center as possible so that the knowledge and skill and competency level of those who are MH experts is offered out to the world as far as we can possibly go.

How do we achieve this level of sharing knowledge? The MH Hotline is a prime example. It is there for others to use 24 hours a day, every day! The MH experts, who share their extensive wealth of knowledge about malignant hyperthermia and how to recognize and treat it effectively, unselfishly give of their skill, which often takes years to develop. In this way, other healthcare professionals can learn and grow in their own capacity to treat MH.

Where else can we make a difference? We ask ourselves that all the time! What is needed by the customers we strive to serve? What have they told us? Where are they frustrated and challenged? We don’t want to try to understand how the possibility of a negative outcome can mentally and physically affect someone; only the person who must deal with this head on can.

To meet this need, the MHAUS Board of Directors gave approval to provide a webinar on the basics of malignant hyperthermia with presenters from both the medical field and also from a family member’s perspective. This was free for patients and their family members to participate in, ask questions and obtain answers they could clearly understand. The reception was very positive resulting in another being planned for July 19, 2017. It was clear we needed to share additional knowledge on the basic genetics of MH, so this became the topic for the July webinar. We encourage MH-susceptibles and their family members to call or email us other topics we should address. We can only identify and focus on your concerns and issues if we hear about them from you.

Other groups MHAUS interacts with on a regular basis are the various regulatory agencies. We either reach out to them due to our need to better understand what they are requiring of the various types of facilities they accredit, or we share the recommendations MHAUS makes with regard to an MH preparedness action plan. Recommendations are open to an individual person’s interpretation and thus become a bit convoluted when being addressed by hundreds of diverse individuals who may have differing interpretations. To try to share the basic premise behind our recommendations and the reasoning for them, MHAUS coordinated a webinar specifically designed to clarify specific MHAUS recommendations for regulatory surveyors’ perspectives. A question and answer period was incorporated and all questions addressed, whether at the webinar or within a few days following it. This open communication between all types of regulatory agencies involved will only help to further each surveyor’s
MH Preparedness Not Limited to OR, Labor & Delivery, and PACU

Preparation and readiness for MH is not limited to the OR, labor and delivery and the PACU.

According to reports, the hospital accrediting bodies (i.e., the Joint Commission) are now looking to see that hospitals are prepared to identify and treat MH in any area where MH triggers might be given, such as the ED, ICU, and endoscopy areas, even if they only have succinylcholine for airway rescue and do not use potent volatile agents on a routine basis. So those areas need to have rapid access to dantrolene and a plan and drill to manage an MH crisis.

MHAUS can help your facility prepare with the MH Prep Check. (When contacting MHAUS, note that the MH Prep Check requires at least two months notice for preparation and coordination).

The MH Prep Check is a nationwide Malignant Hyperthermia (MH) preparedness training opportunity coordinated by MHAUS, specifically for on-site training of healthcare professionals at hospitals, office-based surgery suites, and outpatient facilities, including: anesthesia departments, emergency rooms, medical transport teams, ob/gyn, operating rooms, pharmacy, and scanning facilities.

MH experts will give a 60-90 minute training session including:

- readiness walk-through of the facility;
- on-site MH mock drill; and
- discussion of a facility-specific plan to transfer or receive an MH-susceptible patient to their ER.

The MH Prep Check brings an MH Expert from the elite group within MHAUS who answers emergency MH calls on a regular basis to your facility. Their personal knowledge and direction have saved hundreds of lives. They are available in this program to discuss with the attendees on a one-on-one basis the recognition, diagnosis, and treatment of malignant hyperthermia - the fast-acting hereditary disorder triggered by certain anesthetic agents.

To prepare for the MH Prep Check training, the facility is asked to share feedback with MHAUS about their specific needs. MHAUS will give this information to the MH expert so they are able to tailor the presentation to the needs of each facility. The training will include time for questions and answers. Feedback will be requested to assure we continually improve and address points of concern.

Benefits of holding an MH Prep Check at your location:

- Assurance that participants are prepared for an unexpected case of MH and thus patients are kept safe.
- Clarification of the drugs and equipment needed to address an MH event (as well as their proper use).
- Documentation for Regulatory Surveyors via a Certificate of Participation and listing on the MHAUS website’s MH Prep Report indicating your facility has taken MH preparedness training.

MHAUS has been told that all regulatory agencies use MHAUS recommendations as a barometer for MH preparedness – up to and including taking out a stopwatch to time dantrolene retrieval! Would you pass this test?

The MH Prep Report is also a resource for MH-susceptible patients when researching the best location to manage their future planned surgery. They are very interested in ensuring their medical team is ready for MH.

Register Now for Scientific Conference, Sept. 23-24

Remember to Save the Date and join MHAUS and other malignant hyperthermia experts to expand your knowledge in the world of MH. The 2017 MHAUS Scientific Conference will take place on September 23rd and 24th at the McNamara Alumni Center in Minneapolis, MN

We are making good headway in the preparation of the conference. The agenda will cover RYRI variants, risk of MH in patients with exertional heat Illness (EHI), new approaches to diagnosis and treatment, and a session on raising awareness designed to focus on patients and their families. Dr. Tom Nelson is the Keynote Speaker for this event.

The registration has been set up on the MHAUS website by clicking on the heading “Get Involved” and then the Scientific Conference Event listed on the Calendar heading on the left side.

We have also placed a promotional message on the MHAUS website’s home page. Interested parties will be able to link to the registration page from the slider.

We hope we can count on your help to promote the event so the turnout is the largest yet!

Please feel free to contact the MHAUS office at 607-674-7901 if you have any questions in regards to the conference or visit our website at www.mhaus.org
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Study Concludes Strong Association Between Muscular Male Body Build and MHS

An article appearing in the Canadian Journal of Anaesthesia (64(4):396-401) concludes muscular body build and male sex are strongly associated with MHS.

The article, “Muscular body build and male sex are independently associated with malignant hyperthermia susceptibility,” was written by Brian Butala, Allegheny Health Network, Department of Anesthesiology, Allegheny General Hospital, and Barbara Brandom, North American Malignant Hyperthermia Registry of MHAUS, UPMC Mercy Hospital, University of Pittsburgh.

PURPOSE: Malignant hyperthermia susceptibility (MHS) is a disorder of the regulation of calcium in skeletal muscle. Muscular individuals have been shown to have a 13.6-fold increased risk of death during malignant hyperthermia (MH) episodes and are more likely to experience a recurrence after initial treatment. Twenty-five percent of severe MH episodes have occurred in elite athletes. This study investigated the association between MHS and muscular body build.

METHODS: Data were obtained from existing reports in the North American Malignant Hyperthermia Registry of MHAUS, including the Report of Muscle Biopsy and Contracture Testing (caffeine-halothane contracture test [CHCT]) as well as Adverse Metabolic or Muscular Reaction to Anesthesia (AMRA) reports. Malignant hyperthermia susceptible individuals were compared with MH negative individuals with regard to body build and reason for testing. Males were also compared with females. Both the CHCT and the AMRA forms were reviewed for comments.

RESULTS: Of the 1,292 individuals diagnosed with MHS by CHCT, males were more likely to be diagnosed with the disorder than females (odds ratio [OR], 2.33; 95% confidence interval [CI], 1.99 to 2.7; P < 0.001). Muscular individuals were more likely to be diagnosed with MHS than non-muscular individuals (OR, 1.94; 95% CI, 1.51 to 2.49; P < 0.001). Males were more likely to be tested after having a possible MH episode (OR, 2.33; 95% CI, 1.45 to 2.1; P < 0.001). Logistic regression showed that male sex (OR, 2.28; 95% CI, 1.93 to 2.7; P < 0.001) and muscular body build (OR, 2.17; 95% CI, 1.21 to 3.9; P = 0.01) were independently predictive of MHS. The interaction between muscular body build and male sex was not significant (P = 0.13). Indications for testing, MH episode vs family history of MH, did not differ between muscular and non-muscular individuals (P = 0.44). Eight of 839 AMRAs and two reports of CHCT had comments describing athletic abilities. Ryanodine receptor type 1 (RYR1) gene mutations were found in five of these athletes.

CONCLUSION: Muscular body build and male sex are strongly associated with MHS.

FDA Grants Priority Review for Ryanodex for Treatment of Exertional Heat Stroke

Eagle Pharmaceuticals announced in April that their 505(b)(2) New Drug Application (NDA) for Ryanodex (dantrolene sodium) for the treatment of exertional heat stroke (EHS) has been accepted for filing and granted a priority review designation by the U.S. Food and Drug Administration (FDA).

The FDA grants priority review to medicines that may offer major advances in care or provide a treatment option where no adequate therapy exists. Under the Prescription Drug User Fee Act (PDUFA), the FDA will aim to complete its review within six months of the NDA submission; the PDUFA date for the NDA has been set for July 23, 2017.

“There is currently no approved pharmacological treatment for EHS. If Ryanodex is approved, Eagle will be the first to market with a potentially transformational therapy. EHS can strike anyone, but athletes, our military and outdoor workers are especially vulnerable. We look forward to working with the FDA throughout the review process and to their expedited decision in July 2017,” said Scott Tarriff, Chief Executive Officer of Eagle.
RYANODEX® is formulated for speed and efficiency during the critical challenges presented by malignant hyperthermia (MH)³⁴

- Simple and rapid reconstitution within 10 seconds²
- One-minute administration of a loading dose by 1 provider¹²
- Significantly fewer vials and less IV fluid volume required³⁵
  - One vial of RYANODEX® provides the same amount of dantrolene sodium as 12.5 vials (13 vials reconstituted) of other formulations

RYANODEX®: Because every minute counts³⁴

Choose RYANODEX®:
formulated for rapid reconstitution and administration with fewer vials and less fluid volume.¹

Indications
RYANODEX® (dantrolene sodium) for injectable suspension is indicated for the treatment of malignant hyperthermia in conjunction with appropriate supportive measures, and for the prevention of malignant hyperthermia in patients at high risk.

Important Safety Information
RYANODEX® is not a substitute for appropriate supportive measures in the treatment of malignant hyperthermia (MH), including:

- Discontinuing triggering anesthetic agents
- Increasing oxygen
- Managing the metabolic acidosis
- Instituting cooling when necessary
- Administering diuretics to prevent late kidney injury due to myoglobinuria (the amount of mannitol in RYANODEX® is insufficient to maintain diuresis)

References:

Learn more at Ryanodex.com or call 855.318.2170

Please see Brief Summary of full Prescribing Information on the adjacent page.

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Woodcliff Lake, NJ
RVA-MH-2016-043 7/2016
RYANODEX® (dantrolene sodium) for injectable suspension, for intravenous use.

Brief Summary of Prescribing Information. See Package Insert For Full Prescribing Information

INDICATIONS AND USAGE
RYANODEX® is indicated for the:
• Treatment of malignant hyperthermia in conjunction with appropriate supportive measures (see Warnings and Precautions)
• Prevention of malignant hyperthermia in patients at high risk.

DOSAGE AND ADMINISTRATION (Selected Information)
In addition to RYANODEX treatment, institute the following supportive measures:
• Discontinue use of malignant hyperthermia (MH)-triggering anesthetic agents (i.e., volatile anesthetics and succinylcholine).
• Manage the metabolic acidosis.
• Institute cooling when necessary.
• Administer dantrolene to prevent late kidney injury due to rhabdomyolysis (the amount of muscle in RYANODEX is insufficient to maintain diuresis).

Administration of RYANODEX by intravenous push at a minimum of 1 mg/kg over a period of at least 1 minute, starting approximately 75 minutes prior to surgery. Avoid agents that trigger MH. If surgery is prolonged, administer additional individualized RYANODEX doses during anesthesia and surgery.

Dose for Prevention of Malignant Hyperthermia
The recommended prophylactic dose of RYANODEX is 2.5 mg/kg administered intravenously over a period of at least 1 minute, starting approximately 75 minutes prior to surgery. Avoid agents that trigger MH. If surgery is prolonged, administer additional individualized RYANODEX doses during anesthesia and surgery.

Dose for Pediatric Patients
The recommended weight-based dose of RYANODEX for pediatric patients in the treatment and prevention of MH is the same as for adults for this indication (see Dose and Administration).

Reconstitution and Administration Instructions
The suspension must be reconstituted prior to administration.
Reconstitute each vial of RYANODEX lyophilized powder by adding 5 mL of sterile water for injection (WFI) to be reconstituted as indicated by the pharmacist. To reconstitute with another solution (e.g., 5% dextrose injection, 0.9% sodium chloride injection).
Shake the vial to ensure an orange-colored uniform suspension. Visually inspect the vial for particulate matter and discoloration prior to administration.
Mix the contents of the vial within 6 hours after reconstitution. Store reconstituted suspensions at controlled room temperature (68°F to 77°F or 20°C to 25°C). (For complete Dosage and Administration Section, see full Prescribing Information)

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Muscle Weakness
RYANODEX is associated with skeletal muscle weakness. The administration of RYANODEX as human volunteers has been associated with loss of grip strength and weakness in the legs. Patients should not be permitted to ambulate without assistance until they have normal strength and balance.

RYANODEX has been associated with dysphoria, respiratory muscle weakness, and decreased respiratory capacity in volunteer patients for the adequacy of ventilation.

RYANODEX has been associated with dysphoria. Assess patients for difficulty swallowing and choking.

Somnolence and Dizziness
Somnolence and dizziness can occur following administration of RYANODEX and may persist up to 48 hours post-dose. Patients should not be permitted to ambulate without assistance until they have normal strength and balance. Patients must not operate an automobile or engage in other hazardous activities for 48 hours post-dose.

The concomitant use of sedative agents with RYANODEX may increase the risk of somnolence and dizziness.

Potential for Tissue Necrosis with Extravasation
Care must be taken to prevent extravasation of RYANODEX into the surrounding tissues due to the high pH of the drug. Duration and site of extravasation may be shown by return of venous pressure to the product's prescriptive information. The active comparator was infused at a rate that administered 20 mg of dantrolene per minute for each of the doses evaluated.

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In a study designed to evaluate the safety and tolerability of RYANODEX, healthy volunteers received the intravenous bolus injection over the course of 1 minute for each of the doses evaluated.

The active comparator was an equivalent formulation of dantrolene sodium that differed from RYANODEX in that it contained dantrolene sodium and no mannitol at concentrations of 0.33 mg/mL and 50 mg/mL respectively, which represented the critical component of the product's prescriptive information. The active comparator was infused at a rate that administered 20 mg of dantrolene per minute for each of the doses evaluated.

Table 1 displays the most common adverse events in this study. These data are not an adequate basis for comparison of the types and frequencies of adverse event types between RYANODEX and the dantrolene sodium comparator.

Adverse event increases in frequency with increasing doses in the trial, but not differ in frequency between the two treatment groups. RYANODEX-treated subjects were more likely to report adverse immediate adverse events of flushing, dizziness, and hypotension than those receiving the active comparator.

In all dose groups, hand grip strength declined after dosing. In general, the decline in hand grip strength was more pronounced and occurred more rapidly in the RYANODEX-treated subjects in the 1.0, 1.75, 2.0, and 2.25 mg/kg treatment groups than in the 2.5 mg/kg treatment group, the decline in hand grip strength higher in both this and the 2.5 mg/kg treatment group.

The decline in hand grip strength higher in both the 1.75 mg/kg treatment groups and the 2.5 mg/kg treatment group, the decline in hand grip strength higher in both the 1.75 mg/kg treatment groups and the 2.5 mg/kg treatment group.

Table 1: Adverse Events in Healthy Volunteers

<table>
<thead>
<tr>
<th>Number of Subjects</th>
<th>RYANODEX (n=10)</th>
<th>Dantrolene Sodium Comparator (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>1 (3)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Flushing</td>
<td>8 (27)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (17)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (10)</td>
<td>3 (10)</td>
</tr>
</tbody>
</table>

Postmarketing Experience
The following adverse reactions have been identified during postapproval use of another formulation of dantrolene sodium for injection. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Pulmonary Edema
There have been reports of pulmonary edema during the intravenous administration of dantrolene sodium. The contribution of the dialyzed volume and mannitol in these cases is not known.

Hypersensitivity
Sporadic Reactions
There have been reports of urticaria and erythema possibly associated with the administration of dantrolene sodium for injection. Anaphylaxis has been reported.

Injection Site Reactions
Injection site reactions including pain, erythema, and swelling, commonly due to extravasation, have been reported.

DRUG INTERACTIONS
Calcium Channel Blockers
Cardiovascular collapse in association with malignant hyperthermia has been reported in patients receiving dantrolene in combination with calcium channel blockers. The concomitant use of RYANODEX and calcium channel blockers is not recommended during the treatment of malignant hyperthermia.

Muscle Relaxants
The concomitant administration of RYANODEX with muscle relaxants may potentiate the neurovascular block.

Antipsychotics and Antianxiety Agents
The concomitant administration of RYANODEX with antipsychotic and antianxiety agents may potentiate their effects on the central nervous system (see Warnings and Precautions).

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category C

Adequate and well controlled studies have not been conducted with RYANODEX in pregnant women. However, animal reproduction studies have been conducted with dantrolene sodium. In these studies, dantrolene sodium administered to rats and rabbits produced embryolethality (aborts and decreased pup survival) at doses seven times the human oral dose. RYANODEX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery
In one uncontrolled study, 100 mg per day of prophylactic oral dantrolene sodium was administered to term pregnant patients awaiting labor and delivery. Dantrolene readily crossed the placenta, with maternal and fetal whole blood levels approximately equal at delivery; neonatal levels then fell approximately 50% per day for 2 days before declining sharply. No fetal respiratory and neuromuscular side effects were observed in this study.

Nursing Mothers
Dantrolene is present in human milk. In one case report, low dantrolene concentrations (less than 2 micrograms per milliliter) were measured in the breast milk of a lactating woman during repeat intravenous dantrolene administration over 3 days. Because of the potential for serious adverse reactions of respiratory depression and muscle weakness in nursing infants from dantrolene, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
The safety and efficacy of RYANODEX in the treatment and prevention of malignant hyperthermia in pediatric patients is based on clinical experience with other intravenous dantrolene sodium products, which suggests adult weight-based doses are appropriate for pediatric patients.

Geriatric Use
Clinical studies of RYANODEX did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experiences has not identified differences in responses in the elderly and younger patients. In general, dose selection in an elderly patient should be cautious reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

OVERDOSAGE
Overdosage Symptoms
Overdosage symptoms include, but are not limited to, muscular weakness and alterations in the state of consciousness (e.g., lethargy, coma), vomiting, diarrhea, and crystals.

Management of Overdosage
Emergency general supportive measures are effective for acute overdosage of RYANODEX.

PATIENT COUNSELING INFORMATION
Inform patients, their families, or their caregivers of the following:

Muscle Weakness
Muscle weakness (i.e., decrease in grip strength and weakness of leg muscles, especially walking down stairs) is likely to occur with the use of RYANODEX. Patients should be provided assistance with standing and walking until their strength has returned to normal (see Warnings and Precautions).

Difficult Swallowing
Caution is indicated at meals on the day of administration because difficulty swallowing and choking have occurred with the use of dantrolene sodium products in general. Dysphagia has been reported with the use of RYANODEX (see Warnings and Precautions).

Dizziness and Somnolence
The use of RYANODEX has been associated with dizziness and somnolence (see Warnings and Precautions).

Driving or Operating Machinery
Symptoms such as “dizziness” may occur. Since some of these symptoms may persist for up to 40 hours, patients must not operate an automobile or engage in other hazardous activities during this time (see Warnings and Precautions).

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MH crisis, it also triggered a lifetime commitment of clinical and scientific MH discovery.

Dr. Gronert and his team identified skeletal muscle as the locus for the MH defect, were instrumental in proving the efficacy of dantrolene in the treatment of MH, and recognized that MH susceptible patients could have awake manifestations not associated with anesthesia. Members of Dr. Gronert's team included Denise Wedel, M.D., his successor as the Mayo MH Testing Center Director, Margaret Weglinski, M.D., and Dr. Iaizzo. During the laboratory's peak activity in the late 1980s and early 1990s, it was performing the CHCT three to four times per week. Dr. Wedel also became a significant contributor to the clinical and scientific MH literature, publishing with both Drs. Gronert and Iaizzo.

Dr. Gronert's influence in the world of MH research and testing is evidenced by the number of MH investigators that he mentored, as well as his links to four MH testing sites: the Mayo Clinic (former MH Testing Center); the University of California, Davis (present MH Testing Center; current Director Dr. Timothy Tautz), where he served as Vice-Chair and Director of Research in the Department of Anesthesiology after departing Mayo; the UMN (present MH Testing Center), where his protégé, Dr. Iaizzo, has served as the Director of the MH Muscle Biopsy Center for 27 years; and the Uniformed Services University of the Health Sciences (USUHS, present MH Testing Center) in Bethesda, Maryland, where Sheila Muldoon, M.D., a former Mayo anesthesiology fellow and UMN Masters Graduate, created a testing center over 30 years ago.

Dr. Iaizzo's interest in MH began at the Mayo Clinic in 1986, when Dr. Gronert served as his mentor. From 1987 to 1988, Dr. Iaizzo was the Alexander von Humboldt-Stiftung Research Fellow in the Department of Neurology at the Technical University of Munich, Germany, where he worked with Dr. Frank Lehmann-Horn performing the European version of the CHCT (IVCT). He then returned to the Mayo Clinic for two years before joining the UMN faculty in 1990 to become the Director of the MH Muscle Biopsy Center.

When the Mayo Clinic MH Testing Center closed, Dr. Wedel donated all of the CHCT-related equipment to the UMN. Drs. Iaizzo and William Gallagher were responsible for building this equipment at Mayo. Since 1992, Dr. Iaizzo has performed the CHCT for over 130 patients at UMN. Additionally, Dr. Iaizzo has over 30 MH-related publications, and he is credited with performing numerous MH susceptible swine studies that have advanced our understanding of MH pathophysiology in humans.

Since 1991, Dr. Belani, a Pediatric Anesthesiologist and physician-scientist, has served as the UMN MH Testing Center’s Clinical Coordinator. Dr. Belani became interested in MH as an anesthesiology resident at the UMN in 1977, when he successfully treated a clinical case, and later, when there was a tragic pediatric fatality. A child with urosepsis, who received halothane for anesthesia, died after developing a high fever in conjunction with receiving succinylcholine during intubation for seizures. The possibility of MH was not considered at first, but the child’s father underwent a CHCT at the Mayo Clinic that was positive for MH susceptibility. These two cases piqued Dr. Belani’s interest and motivated him to help establish the UMN as a much needed Midwest MH testing site, as the Mayo Clinic center was closing.

Dr. Belani and his pediatric anesthesiologist colleague, David Beebe, M.D., went on to explore MH associations and MH therapy as they relate to sepsis and thyroid storm in swine models. Drs. Iaizzo and Belani, with colleagues in St. Paul (below), co-directed the last MHAUS Scientific Conference held in Minneapolis in 1996. The keynote speaker at that conference was Dr. Michael Denborough, the physician who published the first article describing MH and its inheritance pattern in 1960. Dr. Denborough traveled from Australia to Minneapolis to deliver his lecture. Along with Drs. Belani and Beebe, other significant contributors to the clinical UMN MH program over the years include Drs. Bruce Cunningham, Jeffrey Chipman, Robert Acton and James Harmon, all surgeons who developed technical mastery in performing the very specialized muscle excision required for the CHCT.

Contributions to our understanding of MH are not isolated to research performed at the UMN Medical School. In fact, some of the most significant scientific breakthroughs occurred at the UMN’s Departments of Animal Science and Veterinary Pathobiology and Biochemistry in St. Paul.

Contributions to our understanding of MH are not isolated to research performed at the UMN Medical School. In fact, some of the most significant scientific breakthroughs occurred at the UMN’s Departments of Animal Science and Veterinary Pathobiology and Biochemistry in St. Paul. Notable contributors include Drs. William Rempel, Esther M. Galant, James R. Mickelson and Charles F. Louis. Dr. Rempel’s integral contribution was in developing the genetically susceptible Pietrain breed of swine used in Minnesota and elsewhere for MH research, along with characterizing alterations in meat quality from these
swine. Dr. Gallant’s expertise using intact tendon to tendon fiber bundles of high viability led to key findings on the aberrant muscle excitation-contraction coupling (regulation of muscle contraction) seen in MH. Concurrently, Drs. Mickelson and Louis used biochemical techniques to examine the mechanisms of calcium regulation by sarcoplasmic reticulum, transverse tubules and the sarcoplasmic reticulum calcium release channel that helped to identify the ryanodine receptor type 1 (RyR1) as the most plausible candidate gene for sequencing and mutation discovery.

The Minnesota connections to MH continue in the present day. Dr. Mickelson is active in exploring canine and equine forms of MH, also associated with RyR1 mutations. Drs. Wedel and Weglinski from the Mayo Clinic are past and current volunteers on the MH Hotline, as are Drs. Belani and Tae Kim at the UMN. Dr. Kim received his certification in pediatric anesthesia from the Mayo Clinic. His expertise is in anesthesia machine preparation for MH. Currently, his research interest is in mining various databases related to MH. John Capacchione, M.D., a Navy trained anesthesiologist, is the most recent addition to the Minnesota MH team. He was mentored by Dr. Muldoon at USUHS from 2004 to 2016, and served as that center’s MH Director from 2012 to 2016 before joining the UMN Department of Anesthesiology in the summer of 2016. His area of research is MH and its association with exertional heat illness, exertional rhabdomyolysis and non-anesthesia-triggered awake manifestations. Additionally, his team at USUHS was instrumental in assisting Eagle Pharmaceuticals in developing RyaneX®, the new highly concentrated formulation of dantrolene.
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knowledge of what MHAUS says and why and, at the same time, MHAUS can hear from the surveyors regarding what their personal frustrations are when they visit a facility to assure patient safety during their accreditation visit.

The knowledge the surveyors provide to MHAUS may very well lay the groundwork for another type of webinar to be presented by MH experts for various types of medical facilities – to share knowledge with them on the basic requirements to deal with an MH event and, perhaps, use what we learn to share specific insight to assure they are better prepared for their next regulatory survey (from the MH perspective, at least). We encourage those of you who would like to see this webinar happen to fill out a contact form and share your support for it, along with the questions you would like to see answered. We will use those contact forms to develop the agenda for the webinar in order to meet the thirst for knowledge and updates that you feel are appropriate for your own particular situation. Let us hear from you either via email, telephone, or by using the contact forms on the MHAUS website designed for this specific purpose. **We don’t know what we don’t know** – tell us what we need to hear from you so we can improve the quality of our service to you.

More specific and highly clinical knowledge will be available in September of this year as well! **The MHAUS-sponsored Scientific Conference will be held September 23rd and 24th in Minneapolis, Minnesota.** There will be several presentations at an intense clinical level, but there will also be a session designed to raise awareness by sharing knowledge and insight on the role of MHAUS and the RYR1 Foundation as well as registries, patients’ and nurse’s perspectives. This conference is only held every 2-4 years, depending on the level of new knowledge available to share; this year there will be much provided. I would encourage everyone to visit our website at www.mhaus.org to register for this conference. I have been told the location is beautiful in September. Why not experience it?

The website will also be sharing an updated In-service Kit which will be accessible from the Internet to download for a specified time period for those who want to place it on their facility’s intranet system. This method to share MH preparedness knowledge has been requested in the past and, until now, the technology was not accessible for us to provide it. We believe we can now share the new option as soon as it is ready. Additionally, there will be updated MH Mock Drill scenarios to integrate new knowledge gained over the past few years, and new options to assist in the treatment plan for an unforeseen MH event. Watch for these products as they evolve to help you be prepared for MH and attain open communication with patients and team members to promote patient safety as the end result.

The level of intellectual property retained by the multiple MH experts within the MHAUS organization, who give freely and unselfishly of their time and energy to assure the knowledge is available to all, is without a doubt the most valuable asset within the MHAUS organization! This has been acknowledged by our customers, members, various agencies and manufactures across North America and beyond!

I encourage you to share the fact that you are a member of this wonderful organization and inspire others to join you in making a difference by becoming a member and, by doing so, obtaining the availability of resources and knowledge that is an integral part of the fiber of our being.

Thank you for sharing your time with me and have a wonderful rest of the summer season!
Did you know?

MHAUS offers a lifesaving Hotline, free-of-charge, for any healthcare professional who unexpectedly comes face-to-face with a malignant hyperthermia emergency and quickly needs help. The cost per call to MHAUS is $100.00, and includes the contracted service to transfer your call to a consultant, the costs associated with the MH Hotline Coordinator, who assures there are consultants ready every day on a 24-hour basis for you. Dedicated MH Hotline Consultants, all well-known MH Experts, freely volunteer their time to help their fellow healthcare professionals through an intense situation.

Consider making at least a $100.00 donation (to cover a single call) specifically to help us maintain this lifesaving tool provided by MHAUS to all healthcare professionals.

Enclosed is my tax-deductible contribution of $_____________ in support of the lifesaving MH Hotline.

Please make checks payable to: MHAUS and send to PO Box 1069, Sherburne, NY 13460.

Yes! I want to support MHAUS in its campaign to prevent MH tragedies through better understanding, information and awareness.

A contribution of: □ $35 □ $50 □ $100 □ $250 □ $500 □ $1000 (President’s Ambassador)

or □ $_____________, will help MHAUS serve the entire MH community.

Please print clearly:

Name: ______________________________________________________________________

Address: _____________________________________________________________________

City: ____________________ State: _____________ Zip: ____________

Phone: __________________________ E-mail: ____________________

I am MH-Susceptible □ I am a Medical Professional

Please charge my □ Visa □ Mastercard □ Discover □ American Express

Name on card: _____________________________________________________________

Credit Card Number: _________________________________________________

CV Code: ____________________ Expiration: ____________________________
THANKS! MHAUS thanks the following State Society of Anesthesiology – Ohio – for its financial support. Our appreciation also goes out to the following Association of Nurse Anesthetists: Illinois. Call the MHAUS office to ask Gloria how your group can join their ranks.

Patient Safety Webinar Online
The MHAUS team in coordination with Dr. John Capaccione and Ms. Lydia Friedman presented a very professional and informative webinar for patients and professionals. It is hoped this will be the first of many. Check out the online webinar video at http://www.mhaus.org/videos.

MH Memorial Ride and After Party, August 26
Join us for a day of fun with the MH Memorial Ride and After Party on August 26, 2017, in Sherburne, NY. Registration begins at Gilligan’s at 9:00 AM. Kickstands up at 11:00 AM for a Sample the Wings Poker Run along Otisco Lake, through scenic Upstate NY with stops at area Pizzeria’s to sample the local cuisine and collect your poker card. Meet back at Gilligan’s for the family friendly After Party that starts at 4:00 PM. The After Party will have a bounce house, ice cream, raffles, and music! All are welcome! Bring the family.

All proceeds from this event will go to MHAUS’ education fund to allow us to continue to educate the healthcare community about early recognition to prevent any more unnecessary deaths from malignant hyperthermia.

Each rider and passenger will receive an event registration kit that includes a meal ticket for the After Party, a t-shirt and necessary registration forms to bring to the event for quicker registration with each online registration. Online registration ends on August 23, 2017.

Registration at the event will include a meal ticket and an event patch. Additional t-shirts and patches will be available for purchase at the After Party. If you have any questions, be sure to contact Tina Roalef at 607-674-7901 or by email at tina@mhaus.org.

Congratulations MH Hotline Consultant Stacey Watt, M.D. will be inducted into the Greater Buffalo Sports Hall of Fame this Fall. She is one of 11 people selected for this prestigious honor.

MHAUS Blog Seeks Contributors
MHAUS monthly blog is open to Board members, the Professional Advisory Council, staff, Hotline Consultants, and MHAUS members-at-large. The only conditions are that the topic relate to MH or MH-like disorders, not exceed 2,000 words, and be appropriate and respectful of all viewpoints. MHAUS invites those interested to comment on MH-related subjects or how MH has affected them and their family. If you have questions or want more information, please email info@mhaus.org.

MHAUS Welcomes New HLCs
The following doctors have joined the MH Hotline: Dorothea Hall, Ronald Reagan UCLA Medical Center, Los Angeles, CA; Ryan Hamlin, Children’s Hospital Medical Center Omaha, NE; and Alan Bielsky, Children’s Hospital Colorado, Aurora, CO.