Malignant Hyperthermia Association of the United States and the
North American Malignant Hyperthermia Registry of MHAUS

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The Communicator

Let's Save A Life

For the first time, the annual MH Mini-Conference is scheduled for two locations this year – Oklahoma City, OK on September 19, and Latham, New York on September 26. The program objectives and registration fees are identical for both conferences.

"Expanding the MH Mini-Conference to two locations is a direct response to the success of past conferences, as well as the feedback we've received from attendees," says Fay Kellogg, MHAUS Fulfillment Administrator.

The conferences will provide updates by medical professionals on current MH research and testing, which includes the latest on molecular genetic testing, as well as address any questions or concerns posed by those attending.

"The mini-conference is a great way for patients and medical professionals to get up-to-date information and direct hands-on experience with the intricacies of dealing with MH," says Ms. Kellogg.

Registration fees are the same for both conferences: $65.00 (on or before September 5 for the Latham conference, and on or before August 29 for the Oklahoma City conference), $75.00 after those dates, $25.00 for patients and family members, $60.00 for three or more family members, and $55.00 for healthcare students. A continental breakfast and lunch are included.

For more information, contact Fay Kellogg at MHAUS at 1-800-986-4287 or email fay@mhaus.org or register online at www.mhaus.org. Credits will be available.

Guest speakers for the Oklahoma City conference are: Tae W. Kim, MD, F.A.A.P., Texas Children's Hospital, Houston, TX, Assistant Professor of Anesthesiology and Pediatrics Baylor College of Medicine, and MH Hotline Consultant for MHAUS; Mohanad Shukry, MD, Children's Hospital of Oklahoma, Oklahoma City, OK, Assistant Professor of Anesthesiology at University of Oklahoma, and a MH Hotline Consultant for MHAUS; and Jennifer L. Geurts, St. Lukes Medical Center, Milwaukee, WI, Genetic Counselor.

Guest speakers for the Latham, NY conference are: Michael G. Adragna, MD, SUNY School of Medicine, Buffalo, NY, Anesthesiologist, Advisory Council for the North American Malignant Hyperthermia Registry, and MHAUS Hotline Consultant for 25 years; Barbara Brandom, MD, Children's Hospital of Pittsburgh, Pittsburgh, PA, Department of Anesthesiology and a MHAUS Hotline Consultant for 18 years; and Deanna P. Steele, Magee Womens Hospital Center for Medical Genetics, Genetic Counselor.

In This Issue:

The Communicator is published four times each year by the Malignant Hyperthermia Association of the United States (MHAUS) and is made possible by a generous grant from JHP Pharmaceuticals, manufacturers of Dantrium®. *The Communicator* is intended to serve the information needs of MH-susceptible families, health care professionals, and others with an interest in MH.

Malignant Hyperthermia (MH) is an inherited muscle disorder which, when triggered by potent inhalation anesthetics and succinylcholine, may cause a life-threatening crisis. The incidence of MH is low, but, if untreated, the mortality rate is high. Since the advent of the antidote drug, dantrolene sodium, and with greater awareness of the syndrome, the mortality rate has decreased. Great advances in our understanding of MH have been made since it was first recognized in the early 1960s, but the nature of the fundamental defect(s) is still unknown.

MHAUS advocates that all surgical patients undergoing general anesthesia should receive continuous temperature monitoring, that adequate supplies of dantrolene be stocked near the OR and that thorough family histories be obtained.

MH Hotline Consultant Workshop Scheduled For ASA Meeting

At this year's American Society of Anesthesiologists meeting, MHAUS will have a workshop on what it means to be an MH Hotline Consultant, drawing on cases from the MH Hotline. Volunteers will play the role of the Hotline Consultant with an actual Hotline Consultant portraying the caller.

"We anticipate the workshop to be open to up to 60 people," said Dr. Henry Rosenberg, MHAUS President. "Not all will be in the hot seat though. Some will be observers and participate in the discussions. There will be two rooms and the session will last for three hours on one day."

Under the direction and mentorship of experienced Hotline Consultants, participants will serve as telephone consultants to simulated practitioners calling with various dilemmas that have actually presented over the years. Each simulated conversation will be followed by a small group discussion.

"We plan to cover diverse topics including MH mimics, masseter spasm, suspected MH in the office/free standing surgicenter, coaching on resource management, and the anxious caller," said Dr. Rosenberg.

MHAUS will soon be rolling out a comprehensive exportable curriculum for MH, and this course would be suitable for potential instructors in simulation centers and other teaching centers, who will be expected to have a high level of mastery of the subject matter.

Hotline Consultant volunteers in the workshop include Dr. Rosenberg, from St. Barnabas Medical Center in Livingston, NJ, Dr. Mary Theroux, from The duPont Hospital for Children in Wilmington, DE, Dr. Kumar Belani from Fairview University Medical Center in Minneapolis, MN, Dr. Charles Watson from Bridgeport Hospital in Bridgeport, CT, Dr. Mohanad Shukry of Children's Hospital of Oklahoma in Oklahoma City, OK.

Goal

Participants will advance their knowledge of the real world presentations of MH and MH-like syndromes in the context of telephone consulting, with its inherent limitations, including lack of visual and environmental cues and lack of non-verbal communication hints.

Objectives

Participants will be able to:

1. Analyze the key elements of an MH-related problem
2. Communicate diagnostic and treatment plans in the treatment of MH
3. Provide guidance in post episode management of MH-susceptible patients
4. Discuss the record-keeping associated with a Hotline call and its relationship to the MH Registry
5. Differentiate MH from other metabolic emergencies in the Perioperative period
6. How the MH grading scale is used in analysis of MH cases
7. Understand how the MH hotline works

The nission of MHAUS is to promote optimum care and scientific understanding of MH and related disorders.

For more information or for materials on malignant hyperthermia or MHAUS' programs, call 607-674-7901; write MHAUS, PO Box 1069, Sherburne, NY 13460; or visit us on the Internet at www.mhaus.org.

Insurance Companies' Refusal To Pay For Genetic Testing Leaves Some With Unexpected Bill

Molecular genetic testing has created new inroads to our understanding and identifying of malignant hyperthermia (MH). But with this medical advance, some families have found themselves stuck with an unexpected bill when their insurance company refuses to pay for the genetic test.

"My bigger concern is that there is still insufficient communication to, or with, families that the process of genetic testing is often not covered (by insurance companies) even when applied for in advance," Dr. Joseph Tobin, MH Hotline Consultant, wrote in a recent online MH discussion message board. "These turn out to be really big costs that families think they are covered for."

In response, MHAUS is including a statement in our publications and web site that reads:

Genetic testing is often helpful in determining whether a patient is predisposed to a medical condition.

However, as with any test, either the patient or his/her insurance company must pay for the test. The cost of the test varies depending on the amount of work involved and on the fee schedule of the laboratory.

Do not take it for granted that because a physician ordered the test and it is a blood test that the insurance company will pay for it.

Many insurance companies consider certain genetic tests as "experimental" and therefore do not pay for the test.

Even if they do, some laboratories refuse to accept the fee schedule of the insurance company, and will ask the patient to first pay up front, then submit their claim to his/her insurance company for personal reimbursement.

Therefore, before having a test done, we strongly suggest you check with both the insurance company and the laboratory as to:

a.) the complete charge for the test, and

b.) whether the insurance company will reimburse you, pay the lab directly, or neither.

Paying for genetic and/or muscle biopsy tests is often a problem. Some health insurance companies will readily cover testing while others will not. MHAUS offers limited financial support to assist those who are advised to undergo genetic testing but do not have the financial resources. Contact MHAUS at 607-674-7901 to learn more about this program.

A genetic test can provide the protection of knowing whether you're MH-susceptible, and genetic testing also helps the medical community better understand MH so that diagnosis and prevention can be improved.

MHAUS is working diligently to promote the development of genetic testing for MH and has sponsored several meetings of scientists interested in the genetic diagnosis of MH. In 2006, MHAUS authorized a grant to Drs. Sheila Muldoon, Khishge Sambuughin and Barbara Brandom for in-depth study of DNA changes to 100 MH-susceptible patients. As well, MHAUS has provided seed money to the clinical laboratories to begin testing patients for known genetic changes related to MH. MHAUS anticipates rapid advances in the genetic diagnosis of MH in the next few years.

You are cordially invited to attend the upcoming

Malignant Hyperthermia Association of the United States

Recognition Reception

in honor of the

2009 Hotline Partnership Award
given to highlight the partnership between a Hotline Consultant and a Medical Professional contacting the MH Hotline for help

Daniel Massik – MHAUS Anesthesiology Residents Award
and

Outstanding Dedication to MHAUS Award

6:00 - 8:30 pm
Monday,
October 19, 2009
Shearton New Orleans Hotel
Bayside C Room, 4th Floor
500 Canal Street
New Orleans, LA

Sponsored by
Malignant Hyperthermia Association of the United States
Please RSVP by September 18, 2009 via phone at 607-674-7901, fax to 607-674-7910 or email to gloria@mhaus.org

Facing Surgery With A Possible Family History Of MH

Sometimes finding answers to your malignant hyperthermia (MH) questions can be difficult (and frustrating), especially if you don't know where, or who, to turn to for answers. The fear and uncertainty that can come with MH is even more acute if you or one of your family members is scheduled for surgery.

Such is the case with Joyce Hall, a 47-year-old wife and mother of two.

"I have a family tree that includes deaths in surgery and a very young death (age 24) from overexertion," she said. "With surgeries in the future for myself and my daughter, I tried many different avenues to get my questions answered, but with no luck."

She first discussed MH with her primary doctor, who referred her to the surgeon, who referred her to the anesthesiologist, who referred her to the MHAUS web site. There she found Bethesda Navel Medical, which happened to be only an hour from her home.

"I started making calls and thankfully found Dr. Sheila Muldoon. She returned my calls and emails promptly. I do not know who I would have turned to if Dr. Muldoon and staff would not step up to the plate," she said.

"My daughter has to have surgery. My brother, twin sister nor myself have ever had surgery. We did not know, based on family history, if surgery was going to be a higher risk than normal for our family members."

– Joyce Hall, 47-year-old wife and mother of two.

Dr. Muldoon is Vice President of MHAUS, Chair of the North American Malignant Hyperthermia Registry (NAMHR) Advisory Council, and Director of the MH Diagnostic Center at Uniformed Services University of the Health Sciences (USUHS). Dr. Muldoon and her staff began poring through Ms. Hall's family medical records.

Ms. Hall's aunt died in surgery in 2004. She also had a grandmother who died in surgery in 1976 at the age of 59. Her uncle (age 24) died in the line of duty as a police officer in 1978 after wrestling with a prisoner.

"We never thought about my uncle's death being related to MH," Ms. Hall said. "Dr. Muldoon asked the right questions."

Ms. Hall was first clued into MH by her uncle's wife, a nurse, who

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through out the possibility of MH after her grandmother's death.

"My daughter has to have surgery," she said. "My brother, twin sister nor myself have ever had surgery. We did not know, based on family history, if surgery was going to be a higher risk than normal for our family members."

Though nobody in her family has been tested for MH, she feels more confident now having her daughter go into surgery, having had her questions answered and knowing what questions to ask her medical professionals.

"Dr. Muldoon has provided us with the answers that only a medical doctor who specializes in this condition could answer," Ms. Hall said. "She was able to understand the medical details and relay them back to me in laymen's terms."

Indeed, the possibility of encountering an MH episode while in surgery, whether it's yourself or a loved one, is a scary thought. But understanding MH and knowing how to prepare lessens the fear.

"Dr. Muldoon has given me a peace of mind and answered questions we have had in our family for years. She has made a difference. Thank you."

Do you have an MH survival story? Tell us about it and include a before and after picture. Visit the MHAUS website at www.mhaus.org and click on "Faces of MH" in the lower left of the patient or professional section, located just above the "Facebook" link.

MHAUS Offers $1,500 Writer's Award To Anesthesia Resident/ Fellow Or Anesthesiologist Within Five Years Of Ending Training

The Malignant Hyperthermia Association of the United States (MHAUS) is pleased to announce the availability of an award in the amount $1500 to the author of a manuscript related to malignant hyperthermia (MH).

In order to promote awareness of MH and its various manifestations and to encourage continued study of the syndrome, Mr. George Massik, a founding member of MHAUS, has graciously offered to support a writers' award. The Daniel Massik Fund at The Foundation for Jewish Philanthropies in Buffalo, NY was established by Mr. Massik in memory of his son who died from MH. This Award will provide a stipend of $1,500 to an anesthesia resident/fellow or an anesthesiologist who is within five years of ending his/her training to attend the annual meeting of the American Society of Anesthesiologists Meeting or, in special circumstances, another meeting of similar merit.

Award Details

The Award will be given to the primary author of the best manuscript concerning, malignant hyperthermia. The format may be a case report, literature review or original study.

- ❑ The document should address a significant issue related to the problem of malignant hyperthermia.
- ❑ Those participating must currently be a resident fellow in anesthesiology or an anesthesiologist who is within five years of ending his/her training.
- ❑ The paper must be a minimum of 3 double-spaced typed pages and a maximum of 10 pages. Author's CV should be included.
- ❑ The paper must not be in any stage of publication.
- ❑ Deadline for receipt of the manuscript in the MHAUS office is August 3, 2009

The award will be presented at the annual MHAUS Recognition Reception at the Annual Meeting of the American Society of Anesthesiologists Meeting in New Orleans October 2009.

The winner will be notified by August 31, 2009 to allow for travel plans.

For further information regarding the application process for this award, please contact the Malignant Hyperthermia Association of the United States (MHAUS), attention Gloria Artist, either via regular mail at P. O. Box 1069, Sherburne, NY 13460, via fax at 607-674-7910 or email at gloria@mhaus.org.

Calsequestrin1 (CASQ1): A New Gene For MH?

You just survived a full-blown MH episode. A muscle contracture test has confirmed that you are, indeed, MH-susceptible (MHS). Your doctor recommends genetic testing to search for a mutation in the ryanodine receptor type 1 (RYR1) gene, the gene most commonly associated with MH susceptibility. If a mutation is found, additional genetic testing for that specific mutation can be recommended for your family, thereby potentially allowing them to avoid the more invasive and expensive muscle contracture test you just went through.

Your test results come back. No mutation in the RYR1 gene was found.

Why is this?

Much progress has been made in the area of genetic testing for MH. Methods to examine the RYR1 gene have improved, and more mutations have been uncovered. However, the sensitivity of the test, that is, the ability of the test to identify a mutation in all patients who are MHS is still low. One explanation is that genes other than the RYR1 gene are responsible for MH susceptibility in some patients.

With this thought in mind, Dr. Robert Dirksen (University of Rochester Professor, scientist and a member of MHAUS' Professional Advisory Council) collaborated with scientists at two universities in Italy to examine the possible role of the calsequestrin type 1 (CASQ1) gene in MH (publication citation: Dainese et al., FASEB J 2009; 23: online).

Why did these scientists look at the CASQ1 gene?

In order to understand their reasoning, a review of some key factors involved in the proper functioning of skeletal muscle is in order.

At the core of skeletal muscle function is a process called Excitation-Contraction (EC) coupling. This process refers to the conversion of an electrical stimulus (an action potential) into a mechanical response, that is, muscle contraction. A key element in the control of the contractile response is the level of calcium ions in the muscle cell. Proper control of calcium levels within the cell is essential for normal muscle function, while alterations in calcium control can lead to muscle dysfunction and disease.

So, it makes sense that scientists looked to examine proteins involved in the regulation of calcium levels to determine whether their function is altered in various muscle disorders.

We know that in skeletal muscle, the type 1 ryanodine receptor (RYR1) gene encodes a protein that serves as a 'channel' through which calcium is released into the muscle cell during an action potential, allowing for subsequent muscle contraction. Further, we know that changes, or mutations, in the DNA code for the RYR1 gene are associated with MH susceptibility.

As a result of the production of an altered RYR1 protein, MH-susceptible (MHS) individuals, may, upon exposure to certain triggering agents such as potent volatile anesthetics (most common) or even heat stress or exercise (less common), be at risk for an MH episode. Exposure of MHS individuals to these triggers may cause an uncontrolled rise in intracellular calcium levels, leading to a prolonged state of muscle contraction, rigidity, an increased rate of metabolism, muscle damage and heat production.

While mutations in the RYR1 gene may account for up to 70% of MHS cases in humans, mutations to other genes likely account for MH susceptibility in the remaining individuals. Thus, it is likely that MH susceptibility also results from mutations to genes encoding other proteins involved in regulating calcium levels during EC coupling. In fact, RYR1 calcium channel proteins are activated during an action potential by another protein, the dihydropyridine receptor (DHPR). Researchers have found that mutations in the DHPR gene can also result in MH susceptibility. However, DHPR gene mutations account for only about 1% of MHS individuals.

Yet another protein, the calse

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questrin type 1 (CASQ1) protein, also regulates intracellular calcium in skeletal muscle. CASQ1 has two roles: one, as its name implies, it binds, sequesters, and stores calcium - that is, it acts like a sponge to soak up excess calcium; its other role is to interact with the RYR1 to modulate its release of calcium. Thus, researchers turned their attention to the CASQ1 protein in an attempt to determine its role in anesthetic and/or heat-induced MH susceptibility.

What did these researchers do?

Dirksen and colleagues utilized genetically engineered mice lacking the CASQ1 protein to determine the role of this protein in MH and MH-like reactions. Mice with and without CASQ1 were exposed to common triggers of MH (eg.,volatile anesthetics) and to less common triggers of MH-like episodes (eg., heat) (Dainese et al., 2009).

What did they find?

Remarkably, exposure of mice lacking the CASQ1 protein to volatile anesthetics and heat stress triggered MH-like crises consisting of whole body contractures, elevated core temperature (108°F), muscle damage, and ultimately, death! Moreover, when the MH antidote, dantrolene, was administered to the mice prior to anesthetic/heat exposure, the MH crises were prevented and the mice survived! Interestingly, the scientists also found that mice lacking CASQ1 were more apt to die spontaneously.

Perhaps even more intriguing was the gender difference observed in these animals: male mice lacking the CASQ1 protein were much more likely to display a trigger-induced MH-like response and were more apt to die spontaneously than their female counterparts. A similar male predominance for MH events has also been reported in the Japanese and North American MH populations.

What does all this mean?

The above-mentioned study has given the scientific community a basis to look further into the potential role of the CASQ1 protein in MH in humans. We do not yet know whether CASQ1 gene mutations are responsible for a subset of MHS patients that lack a mutation in the RYR1 gene. Further, we do not yet understand the reasons for the gender differences in MHS patients and CASQ1 deficient mice and whether or not this reflects a common mechanism. These questions certainly provide ample fertile ground for future basic, clinical, and epidemiological research.

What is next?

Prior to the search for mutations in the CASQ1 gene in MHS individuals, scientists must first conduct 'gene linkage' studies in MHS families that lack a mutation in the RYR1 gene. These studies use genetic markers to narrow the inheritance of a trait (for example, MH susceptibility) within a family to a specific chromosomal location, and ultimately, to a specific gene.

Perhaps such studies will find that in some MHS families lacking a causative RYR1 mutation, a mutation in the CASQ1 gene is indeed the culprit! If this is the case, then the combination of RYR1, CASQ1 and DHPR gene screening should serve to significantly improve the sensitivity of genetic testing for MH.

As a result, the probability of finding a gene mutation to explain your full-blown MH episode will increase dramatically, as will your family's chances of benefiting from this more affordable, less invasive testing option.

The Lila & Jerry Lewis Memorial Fund

There are many special people who take the time each year to remember their loved ones in a way that helps MHAUS. The people below have made gifts during FY 08-09 (July 2008 - June 2009) in memory of Lila and Jerry Lewis. We are most grateful for their support and speical tribute gifts.

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by Marilyn Glassman

MH Hotline Summary – April Through June 2008

by Kumar G. Belani, MD and Preeta George, MD Department of Anesthesiology, University of Minnesota Medical School, Minneapolis, MN.

The Hotline Consultants (HLCs) reported 90 consultations and questions from April to June 2008. There were calls from 38 states and one call from India. Consultants contributing to the group are: Drs. Adragna, Allen, Brandom, Chapin, Gronert, Miller, Millman, Parness, Rosenberg, Chapin, Rosenbaum, Shukry, Skoog, Theroux, Watson and Wong. The majority of callers were anesthesia professionals from hospitals and ambulatory centers. Other callers included a cardiology fellow, five CRNAs, physicians and nurses. Amongst the 90 consults, the HLCs attributed 10 cases with a high probability of malignant hyperthermia.

Syndromes, Muscle disorders and Malignant Hyperthermia

Stuve Wiedermann syndrome is a disorder related to the energy producing organelles in the muscle cell, the mitochondria. The syndrome is lethal at an early age. It is characterized by bone deformities, respiratory distress and episodes of elevated body temperature. The cause of death is often unexplained. This patient presented for a Nissen fundoplication (surgery to correct a deformity of the esophagus and stomach). There is no association with MH. There were questions about other rare inherited muscle disorders, specifically Trisomy-20 and Dandy walker syndrome – neither are associated with MH. There are a large number of inherited muscle disorders where the relation to MH is not clearly known. MHAUS and the Society of Pediatric Anesthesia sponsored a symposium on this subject in 2008. The manuscripts associated with the presentation will soon be published in the journal Anesthesia and Analgesia and should serve as a useful guide for clinicians. However, patients with disorders like cerebral palsy may present with a potentially fatal increase in blood potassium when administered the muscle relaxant succinylcholine. There was one adult patient from Poland that responded as an MH episode and was treated with dantrolene. This patient received the standard dose (2.5 mg/kg), did well but felt extremely weak following dantrolene administration for > 24 hours. This was a report from the ICU. The HLC was surprised by such weakness, although the total dose of dantrolene seemed correct - 220mg administered over 8 hours to a 60 kg adult.

The diseases with a strong association with MH are Central Core disease and minicore myopathy. Familial Periodic Paralysis is also associated and hence it would be prudent to avoid triggering agents in such patients. An elective case with Familial Periodic Paralysis developed jaw muscle rigidity following succinylcholine - the caller was advised to cancel the case and await laboratory investigations and reschedule.

Family History and MH

There were eight questions pertaining to family history and MH. Depending on the family history and after counseling, the clinician may either deliver an anesthetic with drugs that do not trigger MH. Or advise the patient and family to have testing for MH.

Hypertensive crisis with fever

Patients may present with hypertensive episodes and fever with absence of rigidity, acidosis, and no laboratory evidence of hyper metabolism as seen in MH. A patient with coronary artery disease, peripheral vascular disease and chronic obstructive lung disease had a large aneurysm of his abdominal aorta (AAA). He presented for repair of this AAA and during surgery the Hotline was called because of fever along with hypertension and increased heart rate. He had a similar response during cystoscopy one month ago. The HLC discussed the following conditions that could masquerade as MH in such patients: serotonin syndrome, pheochromocytoma, pseudopheochromocytoma, acute renal artery stenosis, hypothalamic stroke, temporal lobe infarct and an immune drug reaction. Since none of these were present in this patient the caller was satisfied and treated the hypertension and fever.

Infection and Sepsis resembling MH

In 23 cases the caller had described patients that the Hotline Consultant thought was not related to MH, but rather to an infectious origin. During these calls the patients were diagnosed with an infective or septic etiology. A 3-year-old presented with multiple dental abscesses for teeth extraction. Following nasal intubation there was a marked elevation in temperature with tachycardia and a rise in end tidal CO2. There were no other signs. Dantrolene was administered before the HLC was called. He was transferred to the ICU and had a purulent discharge from the nose suggestive of bacterial sinusitis. Hence MH was unlikely.

Jaw Muscle Rigidity

Four patients developed a “hard to open mouth” following the admin

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istration of succinylcholine with no other evidence of hyper metabolism. Clinicians need to distinguish between a "hard to open mouth" and a rigid jaw. In the case of the latter, elective surgery should be stopped and the patient observed for signs of MH. In the former the clinician needs to decide if the patient is showing such signs as increased carbon dioxide production, muscle rigidity or other signs of MH. In the absence of such signs, dantrolene administration may be delayed. If relaxation does not occur after surgery and anesthesia the patient may have a diagnosis of TMJ (temperomandibular joint abnormal function). Jaw muscle rigidity, but not spasm, may be due to other causes namely, lighter plane of anesthesia. Masseter muscle rigidity without the muscle relaxant succinylcholine is rare but should raise the question of MH. This certainly warrants observation postoperatively for a minimum period of at least 4-6 hours prior to discharge.

An Unusual presentation

This patient aged 51 had a muscle biopsy diagnosis of MH. His father died of MH and he was on oral dantrolene. The patient developed muscle rigidity lasting for a period of 45-60 seconds triggered with a cough and no associated fever. This patient was advised to go to the ER and evaluated for muscle breakdown, fever and elevated potassium. Unfortunately, we do not have a follow up

Red Herrings associated with MH

A 30-year-old with a traumatic brain and other injuries (no further details available) had an exploratory laparotomy and developed mild metabolic acidosis during surgery but did well. On the eighth post-operative day there was persistent high temperature with a CK >100,000. The Hotline was called at this time and the HLC responded that MH would have intensified or resolved by now and CK could be attributed to muscle trauma. Another, 29-year-old petite lady was scheduled for plastic surgery. She had been anesthetized for two surgeries earlier that were uneventful. When the Hotline was called for this episode, forced air heating was used during anesthesia. An hour after induction her temperature rose to 102 degrees F. No other signs were present indicative of MH-triggering. Warm air heating was discontinued upon the recommendation of the HLC and she did well post-operatively. The HLC concluded that this was iatrogenic overheating and unlikely MH.

Deaths

There were three deaths that were associated with malignant hyperthermia. One occurred in India. The reason for demise was due to the late diagnosis, as MH is thought to be a very rare occurrence in India. Adding to the problem was lack of availability of dantrolene. The other two deaths were related to overwhelming infection in the estimation of the consultants.

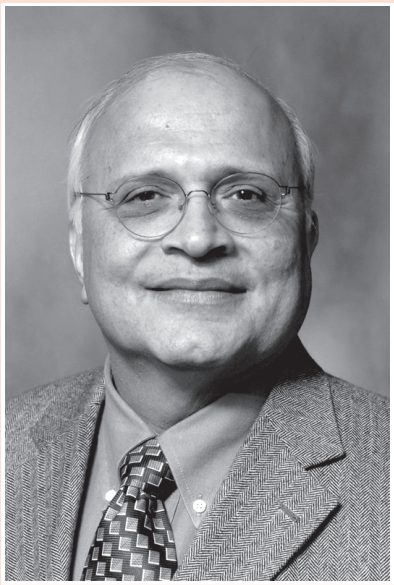
Summary and conclusions

MH or MH-like syndromes may present in a variety of confusing ways. The Hotline Consultants have a large fund of knowledge and expertise to provide guidance, but sometimes there is not enough data to make a diagnosis. In such cases the patients need to be referred for testing. One of the more frequent questions is the relation of MH to other muscle disorders. The information collected through the Hotline and through the North American MH Registry will help clarify the relation of such disorders with MH.

It is also interesting that from time to time calls are received from other parts of the world. It is disturbing to note that many countries do not have access to dantrolene and are ill prepared to deal with the syndrome.

Meet This Issue's Hotline Consultant

Kumar Belani, M.D., Department of Anesthesiology, University of Minnesota, received his Pre University Certificate from Bangalore University in 1968 and his M.B.B.S. from Bangalore University in 1974. He interned at St. John's Medical College, Bangalore University in 1975 and completed his Anesthesiology Residency at the University of Minnesota in 1978. He is specialized in Pediatric Anesthesiology and has been nominated a Top Doctor in the Twin Cities of Minnesota. He has an interest in Global Medicine with a significant role in Public Health and Global Educational Programs.



Dantrium IV And Malignant Hyperthermia History

By Keith O. Ellis, PhD

When I joined Norwich Eaton Pharmaceuticals in 1970, dantrolene had been identified as a skeletal muscle relaxant and was in clinical development for the treatment of spasticity. Mechanism of action work had been focused on polysynaptic inhibition in the spinal cord (e.g., mephenesin-like).

My work delineated the drug action as being directly on skeletal muscle. Further, we defined the mechanism of action as inhibition of calcium release from the sarcoplasmic reticulum in the muscle fiber. In the process of defining the mechanism of action, dantrolene was delivered in a variety of formulations:

- in Krebs/Ringer solution for "in vitro" tissue bath work
- in CMC for p.o. and i.p. delivery
- in a NaOH mannitol solution for iv delivery
- in a wide variety of organic solvents for iv delivery

Autopsies of animals injected with organic solvent iv formulations of dantrolene revealed depots of the drug in the blood vessels walls and in the lungs. The tell tale "dantrolene orange" was visible to the naked eye. Dantrolene has a limited solubility in physiological solutions, and if the drug concentration exceeds that solubility, the drug will precipitate in a tissue bath or in blood vessels.

Ralph White (an organic chemist at Norwich Eaton) and I worked on solubilizing dantrolene for a number of years. We tried different solution techniques, different salts and a wide variety of different chemical structures (new compounds). None proved to be better than one of the first dantrolene iv formulations which was a NaOH mannitol solution.

Dantrolene-induced muscle relaxation was distinct when compared to other agents which produced muscle relaxation. Palpating muscles of animals administered the drug felt like squeezing a bag of water. Animals who were administered large doses of dantrolene (e.g., 1600 mg/kg) were supremely relaxed, yet respiration continued, albeit a very shallow respiration. With dantrolene on board, these animals would have wire cage imprints on their abdomen from days of lying on the screen. Their abdomens had a definitive 'waffle" appearance. This unique respiration sparing muscle relaxation led me to speculate that an iv form of dantrolene would be a clinically useful muscle relaxant. Muscle relaxation - but not muscle paralysis would have utility in a veterinary "field application" where respiratory support was not available.

One of my early experiments was with IV dantrolene in the treatment of tetanus. Tetanus toxin causes sustained cholinergic discharge and consequent continuous skeletal muscle contraction. The muscles eventually rip from their insertions. My hypothesis was that with dantrolene on board the irreversible skeletal muscle damage (particularly the intercostal muscles) would be prevented. I tried to develop an animal tetanus model, to test the hypothesis, but could not stabilize the animals once the tetanus set in.

Dantrolene iv was a drug in search of a disease. Somewhere in this time frame, I read about malignant hyperthermia (MH), the skeletal muscle rigidity and pig model of MH. It was obviously a candidate disease for dantrolene. I wrote to 3 or 4 investigators that I found from literature references to be working with MH pigs and requested information on how I could get MH pigs to test this muscle relaxant drug. I believe one of the investigators was Tom Nelson and one was Gaysford Harrison. The first response was from Harrison who wrote that he could not send me the pigs from South Africa, but if I sent him the drug, he would be glad to test it.

I sent Harrison the dantrolene Na drug supply with instructions on how to get it into solution. The rest is history; as he did the MH pig study that showed dantrolene to be uniquely therapeutic for MH in pigs and published the work in the *British Journal of Anesthesiology*.

The NDA holds records to substantiate this history, as I was employed by the company (Norwich Eaton) in whose name an NDA had been approved for dantrolene sodium (the oral product), and copies of all communications on the subject of dantrolene were kept on file.

After the *British Journal of Anesthesiology* publication, the point person for Norwich Eaton Pharmaceuticals became Mary Kolb. I am not sure of the date when Mary joined the company, but it was a few years after me. She had been managing one of the clinical trials of oral dantrolene sodium in spasticity and was very familiar with the drug.

Gaining approval to do clinical studies of dantrolene in Minnesota was Mary's doing. I remember she had an uphill battle in the company as no one could project a market. It was "interesting", but not a "business opportunity". She eventually received a modicum of support with a budget of $50,000. I remember her remark, "We will see about this," referring to the demimus budget. I suspect she found ways to cover the costs from the overhead in other studies she was managing. Remember, she was setting up trials in North America and Europe in hopes of getting an undefined number of MH treatments with dantrolene IV.

The NDA for dantrolene iv in the treatment of MH was approved by the FDA based on 14 cases, with the FDA pushing for submission ASAP. Dantrolene IV worked, and it did not require any sophisticated statistical analysis to demonstrate that fact.

Mary Kolb deserves more credit than anyone for dantrolene IV being approved for the treatment of MH.

Hotline Panel Discussion Scheduled For The ASA

A panel discussion of Hotline cases will take place October 18, 2009, from 10:30 am to 12:30 pm at the Morial Convention Center Room 343 during the ASA Meeting in New Orleans.

The panel discussion will be moderated by Dr. Barbara Brandom, who will present actual cases along with Drs. Joseph Tobin and Margaret Weglinski.

They will be discussing cases that occurred and were fully evaluated either with post event genetic testing or CHCT. They will, as well, focus on cases that could be done at an ambulatory surgery center.

To learn more about this year's ASA Meeting in New Orleans, please visit www.asahq.org.

Every MH-Susceptible Should Wear A Medical ID Tag

MHAUS has help available for the MH-susceptibles who have no insurance or cannot afford to purchase a medical ID tag.

The Sandi Ida Glickstein Fund was established for the purpose of providing free ID tags for MH-susceptible patients who qualify.

To take advantage of this program, please send us a letter indicating why you would like MHAUS to provide you with a complimentary ID tag.

The goal of the free ID tag program is to ensure the safety of MH-susceptibles during an emergency situation and to prevent a tragic outcome from MH.

For further information, please contact MHAUS at P.O. Box 1069, Sherburne, N.Y. 13460-1069; call 607-674-7901, or visit www.mhaus.org.

Have you visited us lately? Log on to www.mhaus.org to get the latest information on MH, order materials, post a message to the bulletin board or learn about the "Hotline Case of the Month."

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 ❑ (other amount) $ _____, 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: _____
Expiration: _____

Please clip out this handy coupon, or feel free to photocopy if you prefer to keep your issue intact, then mail to: MHAUS, PO Box 1069, Sherburne, NY 13460-1069

MHAUS Happenings, Events and Notices

❑ THANKS! MHAUS is grateful for the financial support of the following State Societies of Anesthesiology: Maryland, Michigan, Ohio. Our appreciation also goes to the following state components of the American Society of PeriAnesthesia Nurses: Kansas, Missouri, and Texas. Call the MHAUS office to ask how your group can join their ranks!

❑ **Upcoming Meetings Being Attended By MHAUS**

The MHAUS staff will be attending a number of upcoming meetings across the country and even Canada. Meetings include: AANA in San Diego on August 9-11; MH Patient Mini-Conference in Oklahoma, OK on September 19; a second MH Patient Mini-Conference in Albany, NY on September 26; and the ASA in New Orleans on October 17-21. We hope to see you there!

❑ **Dr. Steve Howard Joins MHAUS Professional Advisory Council**

Dr. Howard received his undergraduate training at University of California, Santa Barbara in pharmacology. Postgraduate training in anesthesiology at Stanford University School of Medicine followed his medical school training at the Chicago Medical School. He began his academic practice in anesthesiology after residency training and focused his research on 1.) the impact of fatigue on health care personnel and 2.) the impact of realistic simulation on the training and education of health care personnel. He has published extensively on both topics and is also a noted international speaker on these subjects as well.

Dr. Howard is the Co-Director of the Patient Simulation Center of Innovation (PSCI) at the VA Palo Alto Health Care System. He has been a simulation pioneer for nearly 20 years and has used simulation techniques extensively in education, training, and research of all levels of health care providers.

Dr. Howard's expertise in full scale manikin, high-fidelity simulation will be extremely important for MHAUS in the development of modern educational programs.

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Since 1981
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