



The Communicator

Dantrium® Now Supplied By New Company

JHP Pharmaceuticals, LLC (JHP) and SpePharm Holding, B.V. are the new suppliers of Dantrium® to hospitals and surgery centers. JHP will supply Dantrium® to the U.S., Canada, Australia, New Zealand, Israel and Chile, while SpePharm Holding, B.V. will supply Europe and selected other countries.

JHP and SpePharm Holding, B.V. acquired marketing rights from Procter & Gamble Pharmaceuticals, Inc. (P&GP) for Dantrium® (dantrolene sodium) capsules and Dantrium® Intravenous (dantrolene sodium for injection) in August of this year.

In its intravenous form, Dantrium® is used to treat MH (a life-threatening reaction to certain gaseous anesthetics and succinylcholine) and in its oral form, the control of clinical spasticity resulting from upper motor neuron disorders (e.g., spinal cord injury, stroke, cerebral palsy, or multiple sclerosis).

Stuart Hinchin, President of JHP commented, "We are delighted to acquire the rights to Dantrium®. This product will fit well into our current portfolio of marketed products which already includes exports to Canada and Australia."

Jean-Francois Labbe, Chief Executive Officer of SpePharm, said, "We have been pleased to partner with JHP in this acquisition and secure Procter & Gamble's rights to Dantrium® in the rest of the world (excluding the JHP territories). In Europe, Dantrium® will receive sup-

port from SpePharm's growing hospital sales and marketing infrastructure."

To enable product availability during this transition period, the current ordering process will continue through P&GP and the customer service number will remain unchanged (1-800-448-4878) for the next several months. As well, you can order Dantrium® IV directly from JHP by calling or faxing your order to 1-877-547-4547, or emailing customerservice@jhppharma.com.

JHP and SpePharm are in the process of contacting customers regarding the ordering process. No action is required by customers at this time.

Margaret Link, Marketing Specialist with P&GP, said, "Procter & Gamble has determined that Dantrium® intravenous and capsules no longer fit its long-term strategic goals. As a result, P&GP has decided to divest the franchise and redirect resources toward other opportunities."

She added, "Over the past 28 years, P&GP and MHAUS have developed a strong partnership in increasing education of malignant hyperthermia around the globe. P&GP hopes that JHP and SpePharm will also value MHAUS and choose to support their non-for-profit educational goals."

P&GP made its last contribution to MHAUS this spring.

"I had a positive conversation with the president of JHP Pharmaceuticals," said Henry Rosenberg, MHAUS President. "The two principals (Stuart Hinchin and Peter Jenkins) are very

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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 Procter & Gamble 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.

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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.

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ASA Abstract Preview

October 18, 2008

2:00 PM - 4:00 PM, Room Hall E2-Area I

Temperature Changes Are Not Late Signs of Malignant Hyperthermia: A NAMH Registry of MHAUS Study

Marilyn G. Larach, M.D., F.A.A.P., Gregory C. Allen, M.D., FRCPC, Barbara W. Bandom, M.D., Erik B. Lehman, M.S. Department of Anesthesiology, Penn State College of Medicine, Hershey, PA

Goals: Current ASA/CAS standards do not mandate temperature (T) monitoring during general anesthetics^{1,2}. The authors know of 5 MH deaths in young, healthy patients during general anesthetics with no or just liquid crystal (LCT) skin T monitors. In 1987, the North American MH Registry was established to study malignant hyperthermia (MH) epidemiology to improve diagnosis, treatment, and prevention. The AMRA (adverse metabolic and/or musculoskeletal reaction to anesthesia) form gathers data from anesthesia providers. We analyzed AMRA data to determine when T signs occurred and whether T probe type affected time to beginning MH treatment.

October 18, 2008

2:00 PM - 4:00 PM, Room Hall E2-Area I

Serious Complications Associated with Malignant Hyperthermia Events: A NAMH Registry of MHAUS Study

Marilyn G. Larach, M.D., F.A.A.P., Gregory C. Allen, M.D., F.R.C.P., Barbara W. Bandom, M.D., Gerald A. Gronert, M.D., Erik B. Lehman, M.S. Department of Anesthesiology, Penn State College of Medicine, Hershey, PA

GOALS: In 1987, The North American MH Registry (NAMHR) was established to study malignant hyperthermia (MH) epidemiology to improve diagnosis, treatment and prevention. The AMRA (adverse metabolic and/or musculoskeletal reaction to anesthesia) form gathers data from anesthesia providers. We analyzed AMRA data to determine MH complication rate for: consciousness level change/coma, disseminated intravascular coagulation, hepatic dysfunction, pulmonary edema, and renal dysfunction. We studied whether patient, adverse anesthetic, or MH treatment characteristics were associated with serious complications.

October 19, 2008

2:00 PM - 4:00 PM, Room Hall E2-Area I

A Novel Ryanodine Receptor (RYR1) Variant in Two Children with Fatal Spontaneous MH like Events

S. Muldoon, M.D., N. Sambuughin, Ph.D., M. Bayarsaikhan, Ph.D., R. Dirksen, Ph.D., S. Karan, M.D. Anesthesiology, USUHS, Bethesda, Md

Background: Mutations in the ryanodine receptor type 1 gene (RYR1) cause malignant hyperthermia (MH) on exposure to potent volatile anesthetics. Sudden death in people with RYR1 mutations occurs with exertion, high environmental temperatures and febrile illnesses. We present two children who are unrelated but share a RYR1 variant; both died during a febrile illness without exposure to anesthesia.

October 20, 2008

9:00 AM - 11:00 AM, Room Hall E2-Area B

A Novel Minimally-Invasive Malignant Hyperthermia (MH) Diagnostic Test in Swine

Saiid Bina, Ph.D., Rolf Bunger, M.D., Ph.D., Richard C. Kipp, M.D., Fernando Tovar, M.D., John Capacchoine, M.D. Anesthesiology, Uniformed Services University of the Health Sciences, Bethesda, MD

October 19, 2008

2:00 PM - 4:00 PM, Room Hall E2-Area I

The Causative MH Mutation Thr2206Met (Ryr1) May Be Associated with a Mild Myopathy

Henrik Rueffert, M.D., Ralf Schober, M.D., Markus Wehner, M.D., Vera Ogunlade, M.D., Udo X. Kaisers, M.D. Dept. of Anesthesiology and Intensive Care Medicine, University Hospital, Leipzig, Germany

October 19, 2008

2:00 PM - 4:00 PM, Room Hall E2-Area I

Three Mutations in Ryanodine1 Gene in an MH Family

Yasuko Ichihara, M.D., Ph.D., Hirosato Kikuchi, M.D., Ph.D., Keiko Mukaida, M.D., Ph.D., Ichizo Nishino, M.D., Ph.D., Yayoi Narita, M.D., Ph.D. Anesthesiology, Tokyo-Rinkai Hospital, Edogawa-ku, Tokyo, Japan

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October 19, 2008

2:00 PM - 4:00 PM, Room Hall E2-Area I **Volatile Anesthetics Induce Different Contractures in Muscle Bundles of MH Susceptible Individuals**

Thomas Metterlein, M.D., Frank Schuster, M.D., Helga Horbaschek, M.D., Martin Anetseder, M.D., Norbert Roewer, M.D. Department Anesthesiology, University Hospital Wuerzburg, Wuerzburg, Germany

October 20, 2008

9:00 AM - 11:00 AM, Room Hall E2-Area E

Statin-Induced Myotoxicity in Malignant Hyperthermia Susceptible Swine Muscle

John F. Capacchione, M.D., Saiid Bina, Ph.D., Dale F. Szpisjak, M.D., David A. Fish, M.D., Timothy Bruehwiler, B.S. Anesthesiology, Uniformed Services University of the Health Sciences, Bethesda, Maryland

October 18, 2008

2:00 PM - 4:00 PM, Room Hall E2-Area N

Preparation of the Datex-Ohmeda Aestiva Anesthetic Machine for Malignant Hyperthermia Cases

Kelly S. Shinkaruk, M.D., Kevin Nolan, M.D., F.R.C.P.C., Marylou Crossan, B.S. Anesthesiology, University of Ottawa, Ottawa, ON, Canada

October 20, 2008

9:00 AM - 11:00 AM, Room Hall E2-Area B

A Novel Minimally-Invasive In Vitro Diagnostic Test for Malignant Hyperthermia in Humans

Saiid Bina, Ph.D., John Capacchione, M.D., Giovana Tosato, M.D., Rolf Bunger, M.D., Ph.D., Sheila Muldoon, M.D. Anesthesiology, Uniformed Services University of the Health Sciences, Bethesda, MD

October 19, 2008

2:00 PM - 4:00 PM, Room Hall E2-Area I

Skeletal Uncoupling Protein 3 Expression in MDMA ("Ecstasy") Induced Malignant Hyperthermia of Swine

Christiane Hoetzel, M.D., Mark U. Gerbershagen, M.D., Ph.D., MBA, Sascha Burmester, M.D., Ute Schäfer, Ph.D., Frank Wappler, M.D., Ph.D. Department of Anesthesiology and Intensive Care Medicine, University of Witten-Herdecke, Cologne, Germany

October 19, 2008

2:00 PM - 4:00 PM, Room Hall E2-Area I

Is the Skeletal Uncoupling Protein 3 Upregulated in Porcine Malignant Hyperthermia?

Mark U. Gerbershagen, M.D., Ph.D., MBA, Christiane Hötzel, M.D., Jan K. Schütte, M.D., Ute Schäfer, Ph.D., Frank Wappler, M.D., Ph.D. Department of Anesthesiology and Intensive Care Medicine, University of Witten/Herdecke, Cologne, Germany

October 19, 2008

2:00 PM - 4:00 PM, Room Hall E2-Area I

Impact of a Quality Procedure on the Survival of Malignant Hyperthermia Cases

Renee Krivosic-Horber, M.D., Thierry Depret, M.D., Bruno Marciniak, M.D., Lia Mazzoli, M.D., Julia Salleron, Ph.D. Anesthesiology and Malignant Hyperthermia, Hospital Jeanne de Flandre, Lille, France

October 19, 2008

2:00 PM - 4:00 PM, Room Hall E2-Area I

Systemic Effects of MDMA ("Ecstasy") in Malignant Hyperthermia Susceptible and Normal Swine

Jan Karl Schuette, M.D., Mark U. Gerbershagen, M.D., Ph.D., Alexander Starosse, M.D., Sandra Becker, M.D., Frank Wappler, M.D., Ph.D. Department of Anesthesiology and Intensive Care Medicine, University of Witten-Herdecke, Cologne, Germany

You are cordially invited to attend the upcoming

MALIGNANT HYPERTHERMIA ASSOCIATION OF THE UNITED STATES Recognition Reception

In honor of the

2008 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

MHAUS Media Award

6:00 - 8:00 p.m.

Monday, October 20, 2008

Rosen Plaza Hotel

Salon 4 Room, 2nd Floor

9700 International Drive

Orlando, FL

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interested in partnering with MHAUS.”

JHP, (www.jhppharma.com), headquartered in New Jersey, is a specialty pharmaceutical company which manufactures and sells pharmaceutical products, primarily aseptic injectable products into the hospital segment, and provides contract manufacturing of sterile products for innovator pharmaceutical companies. JHP is a private company wholly owned by JHP Holdings, LLC whose equity owners are Morgan Stanley Principal Investments, Peter Jenkins and Stuart Hinchin.

SpePharm Holding, B.V. (www.spepharm.com) is a Dutch company with its registered office in Amsterdam, and its European operations based in Paris, France. SpePharm is an emerging pan-European specialty pharmaceutical company focused on acquiring, registering and marketing high

medical value specialty medicines essentially for the hospital market. Particular areas of therapeutic interest are oncology, critical and support care. SpePharm was founded in September 2006 by Jean-Francois Labbe together with leading life science investment firms, TVM Capital and Signet Healthcare Partners (part of the Sanders Morris Harris Group). Jean-Francois Labbe is a former top executive of Hoechst Marion Roussel and Park Davis with over 30 years of experience in international pharmaceutical management. To date SpePharm has an established commercial presence in the U.K., Germany, Italy, Benelux and the Nordic area where it currently launches its first product, Loramyc, for the treatment of oropharyngeal candidiasis in immune-compromised patients.

A separate company, U.S. WorldMeds, based in Louisville, KY began marketing a generic form of dantrolene last year. (www.usworldmeds.com)

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The Past, Present & Future of Dantrolene

by Henry Rosenberg, M.D.

As all of you know who are reading this, dantrolene sodium, is “the” drug to treat malignant hyperthermia (MH). There are some important and interesting changes and insights developing with this drug that I would like to explore with you.

First, a bit of history: dantrolene was developed by a small company in Upstate NY, Norwich Eaton Pharmaceuticals, not far from our home office in Sherburne, NY, in the early 1970s. A very bright scientist, Dr. Keith Ellis, found that a modification of a drug that Norwich Eaton had developed for the treatment of urinary tract infections, Macrodantin, had rather peculiar properties. When injected in animals, the animals appeared motionless, muscles flaccid, but still breathing. Curious about this, he did some studies in the lab and found that the drug reduced muscle tone, but did not act on the nerves or the neuromuscular junction.

Dr. Ellis had been following the developing malignant hyperthermia story and noted that MH was a disorder involving increased muscle tone and increased metabolism arising from the muscle. He was anxious to test the drug in the MH situation and was put in touch with Dr. Gai Harrison in South Africa who was investigating MH in susceptible swine. He had tried numerous compounds in the treatment of MH, with limited success. When he received the dantrolene compound, he was astonished to see that the drug rapidly and predictably reversed the syndrome.

While I was attending the “Second International Workshop on MH” in Denver in 1975, the news was announced about this wonderful

compound. However, the drug was not yet in an intravenous form, so all sorts of homemade brews were developed using the crushed dantrolene pills.

In about 1982 Procter and Gamble Pharmaceuticals (P&GP) acquired Norwich Eaton and developed the intravenous formulation we know of today. However, the drug had to be approved by the FDA first. So, Mary Elizabeth Kolb was given that task. She arranged for the drug to be available to certain centers and within a few years about 30 cases of MH or presumed MH were collected, scrutinized by a panel (I participated) and concluded that the drug was indeed effective. The drug was approved in record time by the FDA in 1979.

It was one of the seminal advances in the field of anesthesia. (Dantrolene in Human Malignant Hyperthermia: A Multicenter Study. *Anesthesiology*. 56(4):254-262, April 1982.)

Intravenous dantrolene is a difficult drug to get into solution. The compound comes as a freeze dried powder to which sterile water must be added. Furthermore, the drug is packaged in 20mg vials only. For the average person, at least nine vials are needed to be reconstituted and injected. P&GP and their advisors then felt that in order to make sure an adequate amount of the drug was available for treatment of MH, 36 vials should be purchased, no less.

No one could deny that without dantrolene the likelihood of dying from MH was over 50%, but with its use, less than 5%.

So, the company and MHAUS, which was created in 1981, began to urge that all hospitals, ambulatory centers, and office surgery suites using the MH trigger

agents have a full supply of dantrolene available. There must be thousands of patients whose lives were saved by this drug over the years.

This is how the situation stood until 2007 when a start up company, U.S. WorldMeds, LLC began to market a generic version of dantrolene. It was still the same compound.

This past month P&GP announced the sale of its product to two companies, JHP Pharmaceuticals and SpePharm. The former acquired the rights to North America, Australia, New Zealand, Israel and Chile, the latter to Europe and certain other countries. They will work with P&GP to insure that the product is available during the transition. Both companies are committed to providing the drug and perhaps improving its formulation.

Still, there is yet another company, Lyotropic Therapeutics, based in Virginia that has developed a concentrated, soluble form of dantrolene containing 50mg/ml of the drug. This means no more reconstitution and the entire dose can be stored in a syringe. The compound, called *Ryanodex*, has been used to treat and reverse MH crises in swine successfully, but has yet to be approved by the FDA or the European regulators. However, they are moving ahead with product testing. As far as I know it has not been used in any humans to date.

Competition is always helpful in improving products and lowering costs. We now have multiple companies distributing dantrolene and another with a new formulation. This can only be of benefit for those who deal with MH.

Meanwhile, there are some other interesting developments

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regarding the therapeutic value of dantrolene. It has been known for a while that in many cases dantrolene is effective in reversing extreme temperature elevation from a variety of causes. For example, it has been used successfully and sometimes dramatically in the treatment of neuroleptic malignant syndrome and in the treatment of hyperthermia, acidosis and muscle breakdown from drugs of abuse such as MDMA (Ecstasy). An animal model of MDMA toxicity has been developed by researchers Wappler and colleagues from Cologne, Germany and they have demonstrated that Ryanodex reverses the biochemical changes of MDMA toxicity.

Another peculiar and rare syndrome is extreme temperature elevation and muscle breakdown in new onset diabetes in young people. A number of case reports has shown that when this occurs, unless dantrolene is given, fatality is likely. It is not known whether this syndrome occurs in MH susceptibles only or in those who are not MH susceptible.

What is the link between these hyperthermic and hypermetabolic syndromes and dantrolene? Is it a non-specific effect on reducing muscle tone which is capable of generating heat or is it a specific effect of dantrolene's action on the calcium channel (the ryanodine receptor) to which it binds as demonstrated by Dr. Jerry Parness?

Although this is still speculative, the recent finding that the ryanodine receptor is involved in the development of heat-induced MH in the genetically engineered MH mouse, by Susan Hamilton's group, may be informative. (RyR1 S-nitrosylation underlies environmental heat stroke and sudden death in Y522S RyR1 knockin mice. *Cell*. 133(1):53-65, 2008) On exposure to

high environmental temperature leading to high body temperature, a variety of reactive nitrogen compounds are produced that bind to the ryanodine receptor. At least in the mouse model, with the abnormal ryanodine receptor, these compounds will open the channel, thereby releasing calcium into the cytoplasm which leads to all the changes found in MH.

One possibility is that in certain hypermetabolic states, such as those that develop in cocaine and Ecstasy overdose, even with normal ryanodine receptors, the reactive intermediates may alter the ryanodine receptor sufficiently to lead to the typical changes of MH. The investigators, Feige, Wappler and colleagues from Cologne, have shown that MDMA toxicity in even non-MH swine will produce an MH-like picture that is reversed by dantrolene.

One other intriguing hint on this subject: from time to time the MH Hotline is called concerning a young patient who, after open heart surgery, develops hyperthermia, acidosis and other signs of MH but without a family history of MH. If untreated, the patient becomes progressively unresponsive to pressor drugs, develops muscle breakdown and may die. There is one report on such cases published many years ago in the now defunct journal, *The American Journal of Anesthesiology*, by investigators from Johns Hopkins. Another such article by the same authors is "Creatine kinase activity and temperature in children after cardiac surgery."

(*Journal of Cardiothoracic Anesthesia*. 2(2):156-63, 1988.) There were similarities and differences to MH, but none of the patients were tested for MH. Dantrolene reverses this syndrome.

Because this problem is so uncommon and there is no animal model, there is, to my knowledge, no ongoing investigation of the phenomenon.

Another untapped area is the role of dantrolene in heat stroke. Certainly, most heat stroke is not related to MH, but is environmentally induced, but there is definite evidence that some small number of patients who develop heat stroke are MH susceptible.

Unfortunately, this is another area that is virtually devoid of controlled scientific studies, except in the military where the relationship between heat, exercise, and muscle breakdown is under investigation in the laboratory of Dr. Pat Deuster at the Uniformed Services University of the Health Sciences.

With the advent of molecular genetic testing and more widespread awareness of MH and other drug-induced hyperthermic syndromes, we undoubtedly will learn more about dantrolene, its mode of action and its utility in the treatment of disorders other than classic MH.

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MH Hotline Received Over 3200 Calls In Past Year

The MH Hotline continues to be one of our strongest programs, receiving in the past year over 3200 calls. Primary users of the MH Hotline are anesthesiologists and other anesthesia care providers searching for help in handling complex issues involving patient care. Because some of the MH Hotline Consultants are well known by anesthesiologists, they may be called directly by a doctor.

The percentage of accurate MH diagnosis by the caller continues to increase.

"We feel the callers are becoming more and more educated through the educational materials that MHAUS provides, via *The Communicator* newsletter, website, exhibits, and panel discussions given by the Hotline Consultants," says Hotline Coordinator Gloria Artist.

MHAUS is always interested in recruiting and training new Hotline Consultants. Indeed, if you are a current consultant and know someone who you think would be a great addition to the team, contact Ms. Artist at 607-674-7901 or email gloria@mhaus.org.

"Once a consultant has recommended someone," says Ms. Artist, "that person is contacted to get their curriculum vitae (CV) in order to be considered as a possible MH Hotline Consultant. The CV is reviewed by the Hotline Quality Assurance Committee, and a mentor is partnered with the new consultant."

The mentor acts as an advisor the first few times the new consultant takes a call. The mentor reviews and supplies feedback on the content of the reports the new consultant submits during a scheduled two-week coverage period. This feedback is important to the learning process and assures a high degree of quality in the

gathering of important data.

Additionally, the new consultant receives a copy of the Hotline Consultant Handbook, a sample copy of the AMRA form for the North American MH Registry, copies of various other procedural forms and a copy of the most recent Quality Assurance Review.

"We send them the quarterly Quality Assurance Review without the answers and have them review it with their mentor to see how they would respond in the same situations," says Ms. Artist. "This gives them an idea of what kind of cases are coming through on the Hotline and the correct way to handle them."

While there is no official job description, the Hotline Consultant is a highly trained medical specialist who answers phone calls from medical professionals when they encounter MH, or suspected MH, in

the field. Volunteering on rotating shifts, they help callers work through their situations to help them diagnose and treat MH symptoms.

They serve for many different reasons. Some are drawn to help their colleagues, some see the Hotline as a way to further serve and protect patients, and some remember their own first MH experience and want to be that calm voice on the end of the phone for someone in need.

"What I like best about my work with the Hotline is the chance to speak with health care providers from around the country," said Dr. Margaret Weglinski, a Hotline Consultant since 1997, in a recent interview. "Whether it's answering a straightforward question about MH or trying to determine whether or not a patient is experiencing an MH episode, I find it rewarding to (hopefully) be of assistance."

The Lila and 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 07-08 (Oct. 2007 - Sept. 2008) in memory of Lila and Jerry Lewis. We are most grateful for their support and special tribute gifts.

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Greg Glassman & Courtney Grenfell
by Diane & Bob Winters
Honor of the 60th Birthdays of Judy
Levine & Steve Lewis
by Marilyn Glassman

MH Hotline Activity – August – December 2007



by James W. Chapin M.D.

During the months of August through December 2007, 16 volunteer physicians answered 86 calls to the MH Hotline.

Fifty-four involved clinical situations where signs and symptoms indicated the potential for the occurrence of an MH event. Thirty-two calls involved only questions about MH or follow up calls about a previous MH event. Consultants working the Hotline during this period included Drs. Adragna, Allen, Gronert, Litman, Melton, Miller, Millman, Rosenbaum, Rosenberg, Shukry, Skoog, Tobin, Watson, Weglinski and Wong. Eleven of the calls were thought to be probably or definitely MH by the consultants. There were no deaths reported from this group. Nine calls were from a hospital setting. Two were in outpatient surgery centers. All eleven of the probable or definite cases received dantrolene and twelve of the non-MH or unlikely MH calls received dantrolene prior to the Hotline call. Calls came from 32 states, Guam Naval Hospital and the Naval Hospital in Okinawa, Japan.

Elevated CO₂ is an early sign of MH and the skeletal muscle is the source of the CO₂. An excess amount of calcium in the skeletal muscle causes increased metabolism producing extraordinarily large amounts of CO₂ and respiratory acidosis. In addition to MH, elevated CO₂ can be caused by under ventilation, anesthesia machine problems such as exhausted soda lyme (which removes CO₂ from the gas circuit), laparoscopic surgical procedures (there were six reports during this period) where CO₂ is insufflated into

the patient's abdomen to create space to do the surgical procedure. CO₂ is absorbed into the patient's bloodstream. One report during this period was an elevated CO₂ from a coronary artery bypass procedure where they used CO₂ insufflation to harvest a vein from the leg to use for a coronary graft.

Muscle rigidity is a sign of MH reactions. Eleven patients in this group displayed some rigidity. Seven had isolated jaw rigidity; four of the seven had profound jaw rigidity (called trismus) which is highly suspicious for MH susceptibility. Some patients had body or limb rigidity. Some of the cases were cancelled if the rigidity occurred before the surgical incision. Others continued with the operative procedure and switched to non-triggering anesthetic technique. Most of the trismus reports followed administration of succinylcholine, used for muscle relaxation and tracheal intubation. The consultants recommended having the patients with jaw rigidity observed overnight and watched for onset of MH. Then they referred them to an MH muscle biopsy testing center. Two of the rigidity patients were thought to have MH.

There were two calls regarding Neuroleptic Malignant Syndrome (NMS), a condition that mimics MH

but is a reaction to the antipsychotic medications given to patients with schizophrenia. The antipsychotic medications lower brain dopamine levels and some patients develop MH-like symptoms. The antidote is Bromocriptine, which increases the dopamine levels in the brain. Dantrolene can lower the temperature and prevent complications from very high fever. Both calls were referred to consultants who are experts in NMS.

A call was received by a Hotline consultant regarding a patient to be anesthetized later in the day. The patient had polymyositis and was on steroids. The anesthesiologist who called had read in Stoelting's textbook the recommendation of using a non-triggering technique. The caller asked if polymyositis was associated with MH. The MH Hotline consultant said "no." In Stoelting's book "Anesthesia and Co-Existing Diseases," Second Edition, it says: "It has been recommended that drugs capable of triggering MH be avoided in these patients (polymyositis) if the serum creatine kinase is increased." He goes on to say there could be an abnormal response to neuromuscular blockers with enhanced weakness. (Reference: Brown S, Shupak R.C., Patel C: Neuromuscular blockade in a patient with active dermatomyositis. *Anesthesiology* 1992;77:1031-3).

Meet This Issue's Hotline Consultant



James W. Chapin M.D., is Professor of Anesthesiology, University of Nebraska Medical Center, Omaha, Nebraska. He has been on faculty for over 30 years. He has been a Hotline Consultant over 20 years. UNMC was an MH muscle biopsy center for many years. He worked with Dr. Dan Wingard on MH research, and he is Director of Liver Transplant Anesthesia and Anesthesia Residency Program Coordinator.

Some Helpful Malignant Hyperthermia Terms

Creatine kinase

An enzyme found in cells, especially muscle cells. Normal levels are up to about 200 iu/L. In cases of muscle membrane breakdown, the enzyme leaks out of the cell. This may occur from any type of muscle trauma, including malignant hyperthermia. After surgery CK levels may normally rise to 1,000 to 2,000 iu/L. When there is severe muscle damage the level may rise to 10,000 or more. At these levels, the muscle pigment, myoglobin, can be expected to be elevated in the blood as a result of muscle damage. In other words, elevated CK is a marker for leakage of myoglobin from the cell. Elevated levels of myoglobin can lead to temporary or permanent kidney damage. After an episode of MH the CK levels may be mildly or dramatically elevated depending in part on the promptness of treatment. In general, peak levels of CK occur about 24 hours after injury and may be elevated for days. Hence, in suspected cases of MH it is important to determine CK levels. In case of heart muscle damage, CK may be elevated, but this represents a slightly different form of CK. CK from regular muscle is termed CK MM, from heart muscle, CK-MB.

General anesthetics

Compounds that produce loss of consciousness, pain relief and amnesia. General anesthetics are either gaseous agents such as halothane, sevoflurane, and desflurane (all triggers of MH). Nitrous oxide is often used as an adjunct to these agents. It is not a complete anesthetic, and also not an MH trigger. There are a variety of agents that are given intravenously that also may produce anesthesia such as the barbiturates (e.g. thiopental), propofol, and ketamine. None are MH triggers. A variety of other agents are often used during anesthesia such as the narcotics, benzodiazepines (e.g. Valium and Versed) which produce pain relief and sedation.

Local anesthetics

These compounds block transmission of nerve impulses involved in pain sensation. These are the "caine" drugs - novocaine, bupivacaine, lidocaine, mepivacaine. None trigger MH and are safe to use in the MH susceptibles. These drugs are commonly used by dentists, anesthesiologists, pain physicians and surgeons among others.

Molecular genetics

Genetics is the study of inheritance. Molecular genetics is the study of how changes in DNA structure, such as mutations, affect the function of the genes. Molecular, because the

study of DNA entails understanding of molecular or submicroscopic changes.

Muscle relaxants

These are drugs that are more properly termed paralyzing agents. There are two classes of muscle relaxants, non-depolarizing and depolarizing agents based on their mode of action. Typical non-depolarizing agents are vecuronium, pancuronium and rocuronium. None are triggers of MH. However, the one depolarizing agent, succinylcholine is a potent trigger of MH. These agents are administered intravenously and are therefore given by anesthesiologists, emergency room physicians and intensive care physicians.

Rhabdomyolysis

When muscle is damaged and cells are disrupted, the intracellular constituents begin to leak into the blood stream. This includes creatine kinase, myoglobin and the electrolyte potassium. This is termed rhabdomyolysis. This breakdown may be manifested by muscle pain and in extreme cases dark or cola colored urine.

Tracheal intubation and mainstem intubation

In order to control gas exchange during anesthesia a plastic tube is often placed in the trachea (windpipe). This is done usually when the patient is first anesthetized. One end of the tube is connected to a ventilator or respirator to control ventilation. Since the windpipe bifurcates just below the neck line, if the tube is inserted too deeply, the end may go into one of the branches of the trachea (usually the right side) and therefore only one lung will be ventilated. This may lead to a decrease in oxygen in the blood, and rarely an increase in carbon dioxide as well.

LMA – laryngeal mask airway

This device was introduced into practice only a few years ago. The device is often used when tracheal intubation is not needed, but control of the airway is desirable. It is a tube that is so constructed that it does not enter the tracheal but forms a seal around the entrance to the trachea (the glottis). Insertion of the LMA is not as traumatic as insertion of an endotracheal tube and does not require deep levels of anesthesia or muscle paralysis.

Contracture test

This is the test that is used to determine a patient's susceptibility to MH. Muscle is taken from the thigh (about the size of a fingernail) and cut into strips of about one

half inch long and mounted in a chamber and made to contract by electrical stimulation. When the anesthetic halothane is introduced in the chamber the muscle not only contracts but develops a contracture (a sustained contraction). This contracture is typical for MH susceptibles. The drug caffeine may also lead to an abnormal contracture, as may a variety of other anesthetics. Although the test is highly accurate, the inconvenience of the biopsy and the requirement for special technical expertise limits its use.

Neuroleptic malignant syndrome (NMS)

This is a constellation of signs and symptoms marked by high fever, muscle breakdown, acidosis, muscle rigidity and other signs similar to MH. However, the syndrome is induced by drugs used in the treatment of major psychiatric disorders. These drugs include thiorazine, haloperidol (Haldol), olanzapine and other potent antipsychotic agents. The syndrome is not inherited and does not predispose to MH. That is, there is no greater frequency of MH in those experiencing NMS or vice versa. Interestingly, dantrolene is effective in treating NMS. There is no diagnostic test specific for NMS susceptibility.

Reversal agents

There are several drugs that can antagonize or "reverse" the effects of other drugs. The drug, Narcan, or naloxone reversed the effect of narcotics (including the analgesia from these agents). Some drugs, neostigmine and pyridostigmine and edrophonium, reverse the effects of the non-depolarizing muscle paralyzing drugs.

Oxygen saturation

The main purpose of the blood is to carry Oxygen to the various parts of the body along with nutrients and to remove carbon dioxide and other byproducts of metabolism. The amount of Oxygen in a given quantity of blood is not easy to measure, however the saturation level of the hemoglobin in the blood that carries the Oxygen can easily be measured with an external probe attached to a pulse oximeter. Normal Oxygen saturation is above 98%. At levels below about 90% insufficient oxygen is delivered to the blood, which may lead to many problems.

Triggering agents for MH

These are drugs that will lead to the onset of MH. These include all the potent gas anesthetics and succinylcholine.

Social Networking 101: MHAUS On Facebook

by Michael Wesolowski

Social network services focus on building online communities of people who share interests and activities, or who are interested in exploring the interests and activities of others. Major networks such as Facebook, Myspace, Bebo, and Orkut are web-based and provide a variety of ways for users to share e-mail, instant messages, video, and digital images. MHAUS & NMSIS are presently represented on Facebook. This article addresses the basics of Facebook.

Facebook is defined by its creators as: "a social utility that connects people with friends and others who work, study and live around them. People use Facebook to keep up with friends, upload an unlimited number of photos, share links and videos, and learn more about the people they meet."

Though Facebook was only launched in 2004 it has over 50 million active members.

First Step

The first step in joining Facebook is creating a profile. Don't worry, you can control who is able to see each individual part of your profile; just click on privacy located to the top right of any Facebook page. Click on edit settings for any sections you want to modify. Go to www.facebook.com to get started.

Finding Your Way Around

Layout of Facebook is uniform throughout the site. The blue bar across the top of the page will always be there to take you to your own profile, and this is where your friends will be taken if they click on your name anywhere within the site.

Your Profile

Your profile page is where you reside on Facebook. There is a mini-feed which is a summary of your recent

activity on Facebook and is updated automatically.

Friends

Finding friends is the next step, type someone's name in the search box to the top left. If they have a Facebook account then they should be in the list of results. To find them in the future you can either type their name in the search box (links will pop up as you type) or click on the friends' link in the blue navigation bar.

Applications

Applications are programs that operate on the Facebook Platform. You might have noticed a couple of the Facebook applications already: Photos and Groups. The photo application is an easy way to share pictures with friends. Click on the link and you will see some photos from your friends. You can then tag friends in the photo; this is basically letting Facebook know who is in each photo so that the photo can be linked to their profile pages. The group application is fairly self-explanatory. You can browse groups which people have created, join groups, or even create your own. To add applications click the edit link next to applications in the left-hand navigation bar. This is where both MHAUS Cause and Group pages can be found.

In addition, social networks are beginning to be adopted by industry such as healthcare professionals as a means to manage institutional knowledge, disseminate peer-to-peer knowledge and to highlight individual physicians and institutions. The advantage of using a dedicated medical social networking site is that all the members are screened against the state licensing board list of practitioners.

The role of social networks is especially of interest to pharmaceutical companies who spend approxi-

mately "32 percent of their marketing dollars" attempting to influence the opinion leaders of social networks.

A new trend is emerging with social networks created to help its members with various physical and mental ailments. For people suffering from life altering diseases, "PatientsLikeMe" offers its members the chance to connect with others dealing with similar issues and research patient data related to their condition. For alcoholics and addicts, "SoberCircle" gives people in recovery the ability to communicate with one another and strengthen their recovery through the encouragement of others who can relate to their situation. "Daily Strength" is also a website that offers support groups for a wide array of topics and conditions, including the support topics offered by "PatientsLikeMe" and "SoberCircle."

Success

All Social network services rely on people who share interests and activities keeping their content fresh; so if you do join Facebook, make sure to interact often. One way to do that is to stop by the MHAUS Cause Page and write on the Wall. You'll find people from all over the world there, and make sure to ask your friends to join, too. Happy Facebooking!

Do you have an MH survival story? Tell us about it and include a 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.

Slide Show Presentation For MH Risk Available

MHAUS offers a slide show kit (CD-ROM and slide format) with lecture notes on "Managing Malignant Hyperthermia Risk in Today's Surgical Environment." This presentation reviews the risk of MH and assesses current trends in the management of MH in the inpatient and outpatient settings. Two CME credits are available.

This is a valuable tool to assist in developing standard of care practice guidelines and algorithms to ensure patients at risk will have access to appropriate interventions for treating MH. The program is arranged so it can also be used as a self-study program to enhance individual knowledge of MH and the risks involved.

Cost is \$165 plus shipping and handling for the slides and CD. Call 607-674-7901 or visit www.mhaus.org to order.

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: _____

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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: **California, Connecticut, Florida, Illinois, Maine, Maryland, Michigan, Nevada, Ohio and Pennsylvania.** Our appreciation also goes to the following state components of the American Society of PeriAnesthesia Nurses: **Arkansas, Colorado, Delaware, DC, Illinois, Kansas, Maryland, Missouri, Nebraska, New Hampshire, New Mexico, North Carolina, Pennsylvania, Texas, Vermont and Wyoming.** Call the MHAUS office to ask how your group can join their ranks!

□ **NMSIS Announces Promising New Investigators Travel Scholarship for 2008-2009**

The Neuroleptic Malignant Syndrome Information Service

(NMSIS) is pleased to announce a competition to recognize promising new investigators based on a scholarly paper addressing "New insights on psychotropic drug safety and side effects."

Consistent with its mission to advance pharmacotherapy and patient safety, NMSIS offers two travel scholarships to promote education and research by early career psychiatrists. Two prizes of \$2000 and \$1000 will be awarded toward travel costs to attend the American Psychiatric Association Meeting in San Francisco, CA, in May 2009, where the scholarships will be presented.

Papers should address specific issues related to the scholarship theme and be no longer than 15 double-spaced typed pages in length. Literature

reviews, case reports, or original studies that are not in press or published are acceptable. Primary author must be a student, resident or fellow. Papers will be judged on originality, scholarship, relevance and methodology.

To participate, papers and curriculum vitae of the primary author must be submitted by February 6, 2009 to Ms. Dianne Daugherty, 11 East State, Sherburne, NY 13460, fax 607-674-7910, or via email to dianne@mhaus.org.

Winners will be announced by March 6, 2009. Last year's winners were, first place, Dr. Ted Satterthwaite, who authored, "Risk of Extrapiramidal Symptoms with Intramuscular Antipsychotics: A Systematic Review," and, second place, Dr. Alejandra Clark, who authored, "The Use of Antidepressants in Bipolar Illness."

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