



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

Volume 17, Number 3
Summer 1999

The Communicator



Dantrolene Celebrates 20 Years
Dr. Gronert Retires
MH in Japan
Hotline & Registry News

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 malignant hyperthermia.

EDITOR

Katherine O. Riess

Editorial Advisory Panel

Scott Schulman, M.D.
Debra Merritt, C.R.N.A.
Henry Rosenberg, M.D.
Cindy Brubaker, NAMHR
MaryAnn Whitehill

FOR MHAUS

Henry Rosenberg, M.D.
President

Debra Merritt, C.R.N.A.
Vice President for Projects

Ron Ziegler
Treasurer/Secretary

Janice L. Bays
Executive Director

Josephine Nichols
Administrator

Shari L. Williams
Hotline Coordinator

Cynthia L. Solyian
Communications Coordinator

Malignant Hyperthermia (MH) is an inherited muscle disorder which, when triggered by potent inhalation anesthetics and some other drugs, 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.

Dr. Gronert Retirement Raises Funds to Continue His Legacy

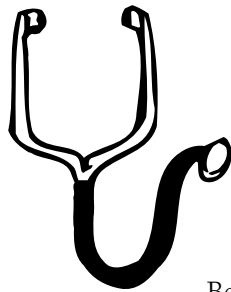
An MHAUS fundraising dinner was held in honor of Dr. Gerald Gronert (*pictured on cover*) for his commitment to the Malignant Hyperthermia Association of the United States, its life-saving hotline, and his continued devotion to researching MH. This event was held at the Riverboat Delta King in Sacramento, CA, on April 24th. There were 82 people present, several of them family members as well as colleagues. Due to the good turnout, MHAUS raised approximately \$1200 to continue the goal of reducing the morbidity and mortality of MH.

Dr. Gronert retired November 1, 1998 from his duties as Vice Chairman and Director of Research for the Department of Anesthesia at the University of

California School of Medicine, Davis, California. In addition to his positions at UC Davis, Dr. Gronert volunteers as a MH Hotline consultant for MHAUS since September of 1983. He is "on-call" 15 days, four times a year to answer calls for the hotline from medical professionals regarding management of potential MH cases.

Dr. Gronert has also been involved in the research of MH since the 1970s. He is one of the investigators who established dantrolene as the specific therapy for MH as well as what triggers MH, the physiology of MH and the appropriate diagnostic test for determining MH. ■

Congratulations to Dr. Brandom



This past year has been a very busy one for Dr. Barbara Brandom of Children's Hospital in Pittsburgh, PA, a Hotline Consultant for MHAUS who also heads our Hotline Review Committee. Dr. Brandom recently achieved her master's degree in biostatistics from the Graduate School of Public Health, University of Pittsburgh. But an unexpected surprise arrived with her diploma. The Omicron chapter of Delta Omega, the National Honor Society in Public Health named Dr. Brandom's thesis "The Best Master's Thesis of the Year in the Department of Biostatistics Graduate School of Public Health, University of Pittsburgh May 1999."

The title was "Assessment of Interaction Between Two Neuromuscular Blockers." Using data on mivacurium and pancuronium, Dr. Brandom examined the expected and observed effects of each alone and in combinations using 3 definitions of interaction: dose additivity, effect additivity and a general method which does not assume that the slopes of the dose response relationships of the two drugs are parallel. The effect of the combination of the 2 drugs was greater than expected only in some analyses which assumed effect additivity. Congratulations!

The Malignant Hyperthermia Association of the United States is a not-for-profit organization dedicated to reducing the morbidity and mortality of malignant hyperthermia and other heat-related disorders by: improving medical care related to MH; providing support information for patients; and improving the scientific understanding and research related to MH and other kinds of heat-related syndromes.

Only MH Antidote: Dantrolene Celebrates 20 Years of Saving Lives



How many members of MHAUS and their families are here today because of the advent of the drug dantrolene? Countless lives have been saved since 1979, lives that would previously

have been claimed by the chain reaction of symptoms known collectively as malignant hyperthermia. Dantrolene, along with the efforts of groups like MHAUS to educate medical professionals of its use, has sent the MH mortality rate plummeting from over 80% to less than 5% last year, according to the MHAUS Hotline reports.

The Advent of a Miracle

In the 1970's, Mary Elizabeth Kolb was a senior researcher for Norwich Eaton Pharmaceuticals (later bought out by Procter & Gamble.) She and Keith Ellis, PhD, are credited with the success of the clinical research that made dantrolene possible.

"Dantrium® IV (dantrolene sodium) provides a unique opportunity to improve a patient's quality of life in the most significant way," says Mark A. Collar, Vice President Global Pharmaceuticals, P & G Worldwide, "by returning them to their loved ones following an MH crisis. We feel fortunate to have a partner like MHAUS educating medical professionals on the importance of being well-trained in MH treatment measures and encouraging adequate stocking of Dantrium® IV (dantrolene sodium) to effectively manage an MH episode."

Dantrolene's important advancement in medicine was recognized in 1989 with the prestigious Claudius Galenus Award. Then,

in September of 1996, MHAUS honored Drs. Kolb, Ellis, and Michael Denborough, the discoverer of MH, for their tireless work in this field.

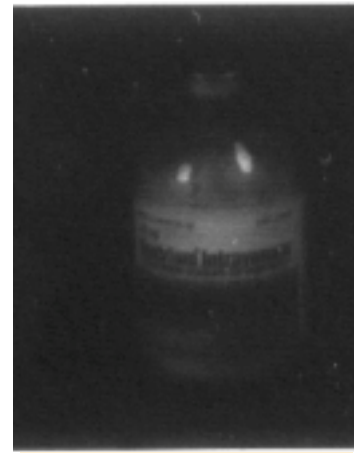
How Dantrolene Works

Prior to dantrolene, when MH would strike, all medical professionals could do was try to cool the patient and treat the individual symptoms. Since dantrolene became available, medical professionals are now able to counteract MH in most cases, because dantrolene is believed to reduce muscle tone and metabolism by preventing the ongoing release of calcium from the storage sites in muscle.

Continuing Education

Of course, we'd like to think that with dantrolene on hand that the unthinkable can no longer happen. But the truth is a *minimum of 36 vials must be stocked wherever surgery is performed*, and more importantly, all medical professionals must be trained to recognize early warning signs and treat MH promptly.

MHAUS congratulates those doctors and nurses who've taken it upon themselves to run drills and training sessions to better prepare their own staffs. In the meantime, MHAUS will continue to provide educational programs and patient support materials to give all those affected by MH a fighting chance. ■



For more information or for materials on malignant hyperthermia or MHAUS' programs, call 1-800-98-MHAUS; write MHAUS, 32 South Main Street, Box 1069, Sherburne, NY 13460; or visit us on the internet at www.mhaus.org.

MH in Japan: News From (JMHA) Japan's Malignant Hyperthermia Association

by Hirosato Kikuchi, M.D., Ph.D.
Chairman and Professor, The First
Department of Anesthesiology
Toho University School of Medicine,
Tokyo, Japan

Members of JMHA

At present, 34 families with a total 49 members are registered members of JMHA. In Japan, even though more than 300 MH crises have been reported since 1960, most of them could not be traced.

Over the past several years, however, many anesthesiologists have begun to contact MH patients and their families and advise them about the muscle biopsy diagnostic test and to register with JMHA.

Activities of JMHA

a. Issuing membership cards (in Japanese and in English) consisting of an ID.No., birthdate, name, gender, MH Hotline and fax number (in Japanese) and a warning notice on the back side concerning agents which should be avoided.

b. Distribution of ID bracelets

c. Creation of a (Japanese) newsletter; the fourth issue was recently delivered to members.

d. Meeting of JMHA : On the

9th of November, 1996, the first meeting of the association was held in Tokyo. Dr. M. Morio delivered a lecture entitled "What is MH?", Dr. O. Yuge, "Statistics of MH in Japan", and I reported on the "MHAUS meeting in Minneapolis". After, we had question & answer session.

e. Medical consultation :

Members often send JMHA medical questions. The JMHA sends these questions to consultant doctors and returns their answers to the members. A frequent question is posed by school administrators regarding the limitations in school activity for MHS students. These questions and answers are summarized in our Newsletter. Another type of request is consultation for medical or dental care, particularly when care is being denied.

MH tests in Japan

There are four MH diagnostic centers in Japan. It is important to note that a test for MH susceptibility different from the European and North American biopsy procedure has been in use in Japan for some time. This test also involves the use of biopsied muscle, but uses a "skinning" technique to strip off the outer membrane of the muscle cell.

Single muscle fibers are used for exposure to caffeine or to small doses of calcium ("calcium-induced calcium release").

In the traditional test used in North America and Europe, muscle bundles are taken through an incision in the thigh about two inches in length. Individual bundles weighing 100-200mg are used and exposed to halothane and caffeine.

With the skinned-fiber technique, the muscle sample is taken

from the upper extremity under local anesthesia with a skin incision of about one inch. Since the muscle sample lasts for 24 hours for this test, the muscle can be transported from a distance.

Muscle samples may be sent from other hospitals. This cannot be done with the traditional test.

However, this test is not used in other centers outside Japan other than for experimental purposes.

Dr. S. Oku, of the Department of Anesthesiology, Shiga Medical College, uses the standard muscle biopsy test based both on the North American Standard Protocol and on the European Standard Protocol. Due to the location of this college, he developed a portable instrument for these tests and on request he visits hospitals and performs the tests. There have been only a few such biopsies performed.

Dr. A. Takagi, Toranomom Hospital, Tokyo, uses the caffeine and halothane sensitivity test.

MH Research Meeting in Japan

Each year, those doing the biopsy and researchers from many other fields with an interest in MH meet to discuss new findings and advances. Findings from the research are published regularly in American, European and Japanese journals.

There is a great deal of interest and effort in understanding the presentations of MH and the molecular genetic basis of the disorder. Malignant Hyperthermia is the subject of a great deal of concern and effort in Japan. ■

This article appears in its entirety on the web at www.mhaus.org.

Dr. Kikuchi started the JMHA in July, 1995, after learning of similar organizations worldwide and the good that they can do for MHS patients.

Q & A: Dantrolene in the Days After MH

Q: *I would like to ask if there is a standard management protocol for subsequent administration of dantrolene once the initial reaction has been treated. Recrudescence develops in 25% of reactions. (Larach, Anesthesiology 79 A 1079) and a variety of regimes are suggested in the anaesthetic literature, e.g. Britt Canad Anaesth Soc J 1984, 61 - an oral regime for 48 hours, Fricker Anesthesiology 89: 1023 - 3 days administration of dantrolene following a reaction. Clinical transplantation 1996: 195 -- intravenous infusion for 24 hours post reaction. Harrison (BJA 60: 279) suggested administration of dantrolene only if the reaction recrudesced and this seems to have been the management in 3 patients in Greg Allen's report (Anes Analg 1998: 86: 1328 -31.) Is there a standard policy to follow? I would be grateful for any comments. Regard, Dr. Neil Pollock, Anaesthetic Dept., Palmerston North Hospital, New Zealand.*

A: I treat subsequent doses of dantrolene on a sliding scale basis. For example, if a patient has trismus after succinylcholine, and recovers immediately and nothing else changes, then no dantrolene. If the patient has some changes in addition to trismus, then dantrolene is used, but no additional doses if the patient remains normal. If the patient suffers what appears to be beginning MH, I follow dantrolene at 1 mg/kg Q 6 hours. If everything has settled to normal after 12 hours or so, I would halt dantrolene. If something recurs, I would give a bolus of at least 1 -2 mg/kg. If a patient is responding well and is still on dantrolene, but shows evidence of worsening, I would add a bolus of at least 2 mg/kg. Dantrolene's half life is long, so control of MH will last quite a while once achieved. -- Dr. Gerald Gronert, UC, Davis, CA.

A: In general, our advice is to give dantrolene for at least 24-48 hours after an episode; longer if there are still signs of MH. The dose once the syndrome is under control is about 1 mg/kg every 6 hours either by bolus or continuous infusion. In fulminant cases, I would go for the 48 hours, for less severe cases, 24 hours.

In addition, I would follow CK at least daily as a crude indicator of ongoing muscle damage.

The basis for our recommendation is not really well-established in the science of MH,

but more in the clinical empirical management of the syndrome.
-- Dr. Henry Rosenberg, President of MHAUS and Residency Director at Thomas Jefferson University Hospital, Philadelphia, PA.

Have a question? Call the office at 1-800-98-MHAUS or email mhaus@norwich.net.

MHAUS recognizes the generous support of

Baxter

Pharmaceutical Products Inc.

1-800-ANA-DRUG

<http://www.baxter.com>

Hotline Activity for July - Sept 1998



During the months of October, November, and December 1998, 11 volunteer consultants handled 71 calls to the MH hotline. Thirty-five calls were case consultations and 36 were questions only.

Sixty-nine calls were from the United States (representing 29 different states) and two were from Canada. Forty-two calls (59%) were made by anesthesiologists, 4 (6%) by certified registered nurse anesthetists (CRNA), and 17 (4%) by a variety of health care personnel including an anesthesia resident, pediatric neurosurgeon, general surgeon, urologist, gynecologist, dentist, pharmacist, recovery room nurse, ICU nurse manager, and pain clinic nurse. The backgrounds of eight callers were not identified. Thirty-five calls (49%) pertained to adults, 23 (34%) to infants and children, and 13 (18%) did not specify the patient's age.

Three Definite MH Cases

Of the 35 case consultations, three cases were designated by the consultant as definite MH and eight cases as probable MH. In five of the 11 cases succinylcholine had been administered; in all but one of the cases a volatile agent had been used. Dantrolene was given in nine of the 11 cases.

One case of interest involved a 38-year-old male undergoing shoulder surgery who was intubated with succinylcholine

and maintained with isoflurane and rocuronium. Following an uneventful intraoperative course and extubation awake, he was quickly reintubated for poor respiratory effort and hypoxemia. Despite aggressive hyperventilation his end-tidal CO₂ remained in the 50's and arterial oxygen saturation remained less than 90%. Ventricular tachycardia developed and was followed rapidly by asystole. Esophageal temperature was noted to be 41°C. He was treated with CPR, dantrolene, active cooling, and a transvenous pacemaker. An arterial blood gas drawn during CPR revealed a metabolic acidosis and a serum potassium of 9.0 mEq/L. Resuscitation was unsuccessful and the patient died.

The caller wanted to know what tests could be done to confirm a diagnosis of MH. The consultant recommended checking a serum creatine kinase and testing the muscle for a subclinical myopathy that might be associated with MH. The family was referred to a biopsy center. Autopsy results were pending. The consultant felt the most likely diagnosis was a fulminant episode of MH during emergence.

22 Cases Thought Unlikely

Twenty-two cases were designated by the consultant as either unlikely to be MH or definitely not MH.

The chief complaint in half of these cases was postoperative fever. Most of these fevers were

ascribed to sepsis, drug reaction, or central nervous system disease. There was one case of rhabdomyolysis and one case of isolated masseter spasm, both occurring after administration of succinylcholine. Both patients were referred for muscle contracture testing.

Three children under age five years received succinylcholine; one received it during a rapid sequence induction for full stomach and the other for management of laryngospasm.

Elevated CO₂ Frequent

Another frequent presenting complaint was elevated end-tidal CO₂. Two of these cases involved patients who were spontaneously ventilating through a laryngeal mask airway (LMA).

The LMA is an upper airway management device that is used as an alternative to the face mask and endotracheal tube. First described in 1983, it surrounds the opening of the larynx as it enters into the back of the throat, rather than passing through the vocal cords as an endotracheal tube does. Therefore, muscle relaxant is not needed to assist in its placement.

Due to its relatively low pressure seal around the larynx and the variable relationship of its opening to the esophagus, spontaneous ventilation is recommended with its use.

One of the cases of isolated increased end-tidal CO₂ was felt to be due to either improper

In the U.S. and Canada, the MH Hotline is 1-800-MH-HYPER. Outside the U.S., call 1-315-464-7079.

placement of the LMA and inefficient ventilation or too small airway disease (patient had a history of asthma). In the other case the increased end-tidal CO₂ was felt to be due to respiratory depression secondary to narcotics.

Most Questions Regard Dantrolene Use in MHS

The majority of the 36 question-only calls handled by the consultants pertained to dantrolene. Most frequently the calls were about the necessity of dantrolene prophylaxis in MHS patients undergoing surgery (not necessary when a nontriggering anesthetic is used).

There were also several questions about the quantity of dantrolene to be stocked in a hospital (36 vials). One caller worked at a hospital where succinylcholine was occasionally given in the emergency room, but no surgical procedures were performed there. The consultant advised that MHAUS recommends that dantrolene be available wherever general anesthesia is administered, and although it is not administered at the caller's hospital, ideally it would be wise to have dantrolene on hand in the emergency room.

Things That Resemble MH

Several questions centered around MH and its possible association

with other diseases: arthrogryposis (no), amyoplasia congenita (no), occulocranio-somatomyopathy (no), Charcot-Marie-Tooth (no), osteogenesis imperfecta (no), and central core disease (yes).

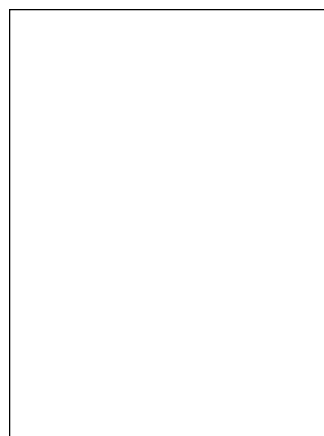
Inquiries regarding the safety of various medications in MHS patients were received: local anesthetics mixed with epinephrine, iodinated contrast dye, belladonna drugs, gabapentin (Neurontin), clonidine, and selective serotonin reuptake inhibitors. All were deemed safe for MHS patients.

Calcium Channel Blockers

Two calls pertained to the use of dantrolene in patients who are chronically taking calcium channel

blockers. In swine, the administration of dantrolene and verapamil (a calcium channel blocker) was shown to lead to hyperkalemia and cardiovascular collapse (*Anesth Analg* 63:473-8, 1984). Dantrolene induced hyperkalemia in a human MHS patient taking diltiazem (a calcium channel blocker) and metoprolol (*J Cardiothorac Anesth* 2:363-6, 1988). Patients with heart disease or hypertension who are taking calcium channel blockers may be at higher risk from dantrolene administration. Dantrolene should be infused slowly and serum potassium levels and cardiac function monitored carefully in such patients. ■

Meet This Issue's Consultant



This issue's Hotline Activity was summarized by Dr. Margaret Weglinski, a consultant for the Department of Anesthesiology as well as an Assistant Professor of Anesthesiology at the Mayo Clinic. Dr. Weglinski has been doing muscle biopsies with Dr. Denise Wedel, also at Mayo, since 1991, and became a Hotline Consultant for MHAUS in 1997. She lives with a "big dog," and says she values the work she does with malignant hyperthermia because, "I like working with MH patients undergoing evaluation for the possibility of MH susceptibility because it gives me the opportunity to get to know them better and their families members. Often," she adds, "it leads to a longer term relationship, and I find that very rewarding."

MHAUS Happenings, Events and Notices

❑ **The (NAMHR) North American Malignant Hyperthermia Registry** is continuing its efforts to identify families suitable for genetic testing. We are interested in hearing from families, especially those who have had the diagnosis of MH established in more than one family member, and in more than one generation.

The Registry has acquired new software, called Cyrillic, to help us in this endeavor. The Cyrillic software, which is widely used by genetic scientists in Europe, will enable us to plot family trees.

If you wish to participate in this on-going study, please contact Cindy Brubaker, Database Manager, at (717) 531-6936.

❑ **MHAUS Medical Identification Tags Now Available:** Do you want the peace of mind that the MH Hotline will be called FIRST if you or your MH-susceptible loved ones are in an emergency? The new tags are imprinted with the MH-Hotline number to connect ER personnel immediately with your history. Call 1-800-98-MHAUS for more information about the new MH ID program.

❑ **If you plan to travel this summer:** Make sure you get a copy of the MH Travel Brochure, a guide with phone numbers of the MH experts in many countries world-wide to give you peace of mind no matter where you go. Call the MHAUS office at 1-800-98-MHAUS for a copy, and enjoy your vacation!

❑ **Will Your Employer Match Your Gift to MHAUS?** Many businesses and corporations have “matching contributions” programs. These programs are set up as a means for an organization to support its employees by supporting the employees’ personal charitable interests.

Some matching programs are 100% matching. This means the employer will “match” each dollar the employee donates. If the employee contributes \$50 to MHAUS, for example, the employer will also contribute \$50 to MHAUS.

Check with your personnel department to see whether your employer will match your gift to MHAUS. If not, then suggest a matching program be set up. Remind them the employer’s contribution is tax-deductible, too!

postage paid
non-profit
organization
permit #339
stamford, ct 06094

MHAUS
32 South Main Street
P.O. Box 1069
Sherburne, NY 13460-1069

