Malignant hyperthermia

Beverley A. Britt MD FRCPC

Malignant hyperthermia (MH) is a pharmacogenetic disorder characterized by acute hypercatabolic reactions in muscles in response to the triggering effects of certain drugs (used mainly during anaesthesia) and stresses.

Epidemiology

MH crises occur in man, pigs, and also in a few other species such as cattle, greyhounds, racehorses and giraffes.[1] In humans, the trait is rare, but not absent, below the age of three years. A very few cases have been reported in newborns. The maximum incidence lies between the ages of three and 30 years. Above this age, the frequency of occurrence of MH reactions gradually declines. No cases have been reported after the age of 78 years.[2] Among teenagers crises are more common in males than in females.[2,3] This sex difference appears to be due to the fact that males have larger, stronger muscles and take part in more high risk sports. They therefore require more anaesthetics and their larger, more active muscles are more susceptible to the triggering influences. When trauma cases are deleted from the total, the incidence of MH reactions is about evenly distributed between males and females.

About half of those who have had MH reactions have also had other previous anaesthetics, about half of which have been apparently normal. The record is twelve previous normal anaesthetics with triggering drugs, and then a fatal reaction on the thirteenth anaesthetic. A previous history of normal anaesthesia, therefore, does not rule out the possibility of a future malignant hyperthermic reaction.[2,3]

All racial groups are affected with MH. The incidence is higher in Japan (1:7,000 to 1:110,000) than in North America (1:15,000 to 1:150,000).[4] While MH has been observed in North American Blacks, it has never been reported in Africa north of South Africa and in South Africa it has been described only in mixed race and Caucasian patients. It is not certain whether these geographical differences are due to racial, climatic or reporting variations.

In some families, the mode of inheritance is clearly a single, autosomal dominant gene. However, in other families the pattern of inheritance would appear to be recessive, and in still others, multigenic.[5] In favour of the latter postulate is the observation that the MH trait does not exhibit uniform severity. Rather, in terms of reactions, abnormalities in tissues and cells of mesenchymal origin, screening and diagnostic tests, MH is a spectrum ranging from the very mild to the very severe. Individuals not infrequently resemble the mean of their parents' patterns rather than segregating into one parental type or the other. Furthermore, within families a mosaic may exist in that one individual may exhibit one feature of MH but not another, while the reverse may often be true for another family member.

Triggering drugs

Drugs capable of triggering MH reactions during anaesthesia include any of the potent inhalational agents (halothane, enflurane, isoflurane, methoxyflurane, trichloroethylene, chloroform, diethyl ether, ethylene and cyclopropane) and any depolarizing skeletal muscle relaxant (succinylcholine).[6,7] In pigs, large doses of intravenous caffeine can trigger fatal reactions. Sympathomimetics and parasympatholytics are able to aggravate already established reactions. An excess of endogenous norepinephrine may be the immediate trigger of stress-induced reactions. There have been a few reports of very large volumes of amide local anaesthetics triggering MH reactions, but in virtually all such cases, a sympathomimetic was also present in the amide local anaesthetic. Other drugs that elevate myoplasmic calcium, such as cardiac glycosides and calcium salts, may also exacerbate MH crises.[2,6] Rarely, halogenated *x*-ray contrast media such as Diodrast have precipitated MH crises.

Departments of Anaesthesia and Pharmacology, University of Toronto; Toronto General Hospital, Toronto, Ontario, Canada.

Stress-induced MH reactions

Stress, with attendant exposure of the muscles to excess norepinephrine, plays an important role in the genesis of reactions in both pigs and humans.[8,9] Stress reactions may be triggered by strenuous and prolonged exercise or extensive skeletal muscle injury, particularly in very hot and humid weather, or under emotionally stressful conditions. These summer-type reactions closely resemble heat stroke in that they are typified by transient dizziness and muscle pain, followed by coma, hyperthermia, muscle rigidity, tachycardia, ventricular arrhythmias, metabolic and respiratory acidoses, hyperkalaemia, creatine kinase (CK) elevation, and perhaps moderate myoglobinuria.

During the winter, shivering induces reactions which, if severe, are marked by a much slower onset of muscle pain, weakness, malaise, sweating, marked CK elevation, severe myoglobinuria leading to renal failure and rapid muscle wasting. More commonly, in the winter mild stress-induced MH reactions are typified by persistent low grade muscle and joint aches and pains, sensations of muscle weakness, malaise and sometimes, though not always, low grade fevers, headaches and moderate CK elevations. These winter-type reactions are much more common in Canada than in the southern United States. Before and after anaesthesia, stress is also a factor. If the patient comes to surgery very apprehensive, having suffered trauma, infection, or violent exercise in the immediate past, he is more likely to have a MH crisis and the crisis is more likely to be severe. In the recovery room, if pain, agitation or shivering are allowed to occur, then a MH reaction may develop, even though perfectly safe agents had been used during the anaesthetic. Many of these recovery room reactions are relatively benign. Probably the majority of MH reactions actually occur in the recovery room but are missed or misdiagnosed.

Anaesthetic-induced MH reactions

Early signs

Until recently the most typical and consistent early sign observable during an anaesthetic reaction was tachycardia. However, with the advent of end tidal CO_2 analyzers, the earliest observable sign is now a rising expired CO_2 tension. Other early signs are unstable blood pressure (usually trending in an upward direction), soaring cardiac output, and ventricular arrhythmias, beginning with occasional ventricular extrasystoles and then progressing to bigeminy and finally to ventricular tachycardia.

Rigidity is the most unique of all signs, but it is not always present, may not develop until late, and then the rate of onset may be only very gradual. Most typically though, rigidity begins immediately and rapidly after infusion of succinylcholine, with the first perceived sign being masseter jaw spasm. Rigidity is more apt to occur if the succinylcholine has been given after commencement of halothane. This may be why masseter jaw spasm is so much more common in the United States than in Canada, because in Canada, anaesthesia for children generally begins with a thiopentone, succinylcholine, intubation, halothane sequence, whereas in the United States, the protocol for children is more usually a halothane, succinylcholine, intubation sequence. In a number of mild and/or rapidly aborted MH reactions, masseter spasm may be the only abnormality observed, especially in children.[2–4,8–10]

In contrast, a very mild reaction may be characterized by only a moderate tachycardia and fever, with no rigidity at all, especially in adults. Profuse sweating and a bright red flushing of the skin may be followed by a rather peculiar mottled cyanosis that is mainly due to intense peripheral vasoconstriction and partly to a widening of the arterial-venous oxygen tension gradient. If the patient is breathing spontaneously, the respirations may be rapid and deep and the soda lime, if it is being used, becomes usually hot and discolored. Fever tends to develop rather late, as it is a result of all the various biochemical dearrangements in the muscle, not a cause. The time of onset of fever and its rate of rise are quite variable, extending from a few minutes after induction to several hours after the patient leaves the recovery room. The rate of rise ranges from less than 1° to over 30° C per hour.[2–4,8,9]

Laboratory features

Very early sharp rises in serum calcium and potassium occur and are followed by profound and prolonged reductions in these ions which may last several days, whereas serum phosphorous and magnesium and blood glucose elevations persist. Increases in acid waste products of metabolism such as CO_2 and lactic acid cause respiratory and metabolic acidoses, particularly of the venous blood. Venous pHs, therefore, fall to very low

levels. Somewhat later, myoglobinemia and then myoglobinuria develop, causing a red or brown urine followed by oliguria and a rising blood urea nitrogen (BUN) if the reaction is poorly treated. In a well-treated reaction, reduction in renal function, should not occur. Serum CK and other muscle enzymes rise rather late, if dantrolene has not been administered. Rarely, CK values in excess of 1,000,000 units have been reported and values above 100,000 units are not uncommon.[2-4,8,9] If dantrolene has been given, then these enzyme elevations may be attenuated or even absent.

Late complications

Late complications, in addition to renal failure, include acute pulmonary oedema, consumption coagulopathy and encephalopathy with cerebral oedema. These occur partly as a result of the temperature, acid base and electrolyte dearrangements, but also because of a primary defect occurring in tissues other than skeletal muscle. For instance, at least in part, pulmonary oedema develops because of MH in the muscle cells of the left ventricle, consumption coagulopathy because of MH in the platelets and neurological deterioration because of MH in the brain cells. Other late complications, though fortunately non-fatal, are skeletal muscle oedema and generalized muscle pain.[2-4,8,9]

Differential diagnosis

Malignant hyperthermic reactions must be differentiated from other conditions that may produce fever during anaesthesia;

1 Decreased heat loss due to the covering of patients with heavy drapes.
2 Increased exogenous heating by a too hot heating blanket or by a malfunctioning ventilator.
3 Increased internal heat production due to:
   (a) excessive shivering in response to cold or struggling;
   (b) endocrinopathies such as phaeochromocytoma or thyrotoxicosis;
   (c) osteogenesis imperfecta;
   (d) infection, either pre-existing or induced by infusion of infected blood, by intravenous fluids or by contamination of the wound site;
   (e) mismatched blood transfusion.
4 Combined decreased heat loss and increased heat production due to:

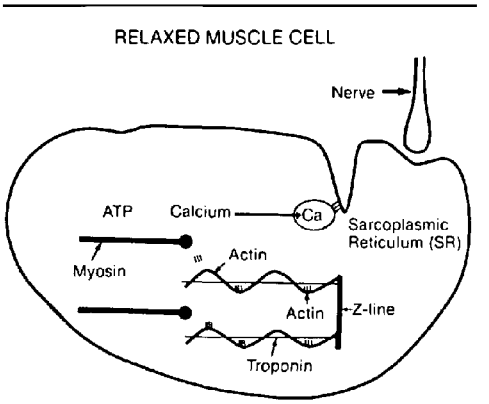

FIGURE 1 Normal muscle cells alternate between being "relaxed" (Figure 1) and "contracted" (Figure 2).

   (a) an abnormality of the central temperature regulating mechanism in the hypothalamus secondary to an intracranial lesion, e.g., head injury, or exposure of the hypothalamus to prostaglandin E or 5-hydroxytryptamine.
   (b) idiosyncratic response to psychoactive drugs, e.g., glutethimide, monoamine oxidase inhibitors, amphetamines, butyrophenones, tricyclics, and phenothiazines. This type of response has recently been termed the Neurolept Malignant Syndrome (NMH).

Aetiology and pathophysiology (Figures 1 and 2)

The precipitating cause of a MH reaction has been postulated to be a sudden rise in the concentration of calcium in myoplasm in the presence of a triggering agent.[10,11] This postulate has been confirmed recently by microelectrode studies performed by Lopez *et al.*[12] The excess calcium is derived from the sarcoplasmic reticulum (SR). Either calcium uptake, calcium binding or calcium release could be abnormal in MH muscle.[11,13] Investigations of the former two possibilities have been contradictory. More recent studies on calcium release from the SR have been much more consistent and have clearly shown that calcium release, in the presence of triggering agents such as halothane, is greater from MHS SR than from normal SR.[14] Such excessive "leakiness" of the SR may be due to a primary defect in the membrane of the SR or to a primary defect originating in some other part of the muscle cell, for instance, the mitochondria, the excitation–

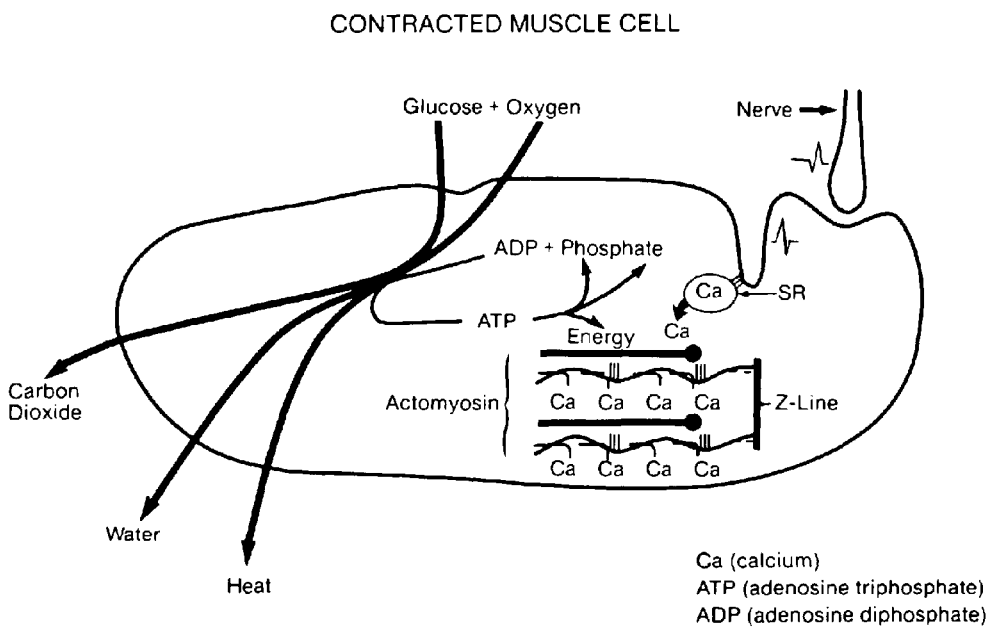

FIGURE 2 In an MH reaction, the muscle cells remain "locked" in the contracted state (Figure 2), producing excessively large amounts of CO_2, H_2O and heat. On the other hand, production of ATP ceases.

contraction coupling step, the transverse tubules, the sarcolemma or the catecholamine innervation pathway.

It has been shown that both caffeine- and calcium-induced calcium release from MHS SR are much greater than from normal SR.[15,16] The latter is unquestionably of greater physiological import in the genesis of *in vivo* MH reactions. The source of the exogenous cytoplasmic calcium which triggers release of the endogenous SR calcium has not been established, nor has the reason for the excessive sensitivity of the MH SR to exogenous calcium. It has been postulated that the calcium channels of the SR are rendered superpermeable because of a defect in their structural phospholipids, a defect induced by excessive and/or abnormal phospholipases originating in the mitochondria.

In mild MH reactions moderate releases of calcium from the SR to the myoplasm that are insufficient to activate the contractile apparatus, are, however, able to activate metabolic processes, for instance, by accelerating conversion of phosphorylase b to a, thereby stimulating production of heat, CO_2, lactic acid and consumption of oxygen.[3,6,8,10,11,13]

In more severe MH reactions still higher myoplasmic calcium levels activate myosin ATPase and SR ATPase, thereby increasing heat production by accelerating the hydrolysis of adenosine triphosphate (ATP). Additionally, the elevated myoplasmic calcium inhibits troponin by opening up small gaps in this monomer through which myosin cross bridges are able to contact actin receptors, so permitting myosin to slide over actin to form short and rigid actomyosin. Finally, calcium is taken up into the mitochondria where it uncouples oxidative phosphorylation so that ATP production ceases while formation of carbon dioxide, water, heat, lactic acid and consumption of oxygen all increase still further. Initially, myoplasmic ATP levels are reasonably maintained because of conversion of creatine phosphate (CP) and ADP to creatine and ATP. Once the cell's stores of CP are consumed then muscle ATP levels also decline. No substrate then remains for the various pumping enzymes of the cell membranes, for example, for Na^+ K^+

ATPase of the sarcolemma and Ca^{++} ATPase of the SR.[3,6,8,10,11,13] Once ATP has disappeared from muscle, therefore, further treatment of the patient is probably futile.

Malignant hyperthermia – a widespread membrane defect

MH appears to be a widespread membrane defect involving both different membranes within the same cell type as indicated above, and membranes of different cell types. While the most adverse expression of the trait is in the skeletal muscles, considerable evidence suggests that heart muscle, smooth muscle, motor nerves, brain cells, platelets, lymphocytes, erythrocytes and cells of the Islets of Langerhans may also be altered by the MH defect.

Preanaesthetic diagnosis

History and examination

Diagnosis of MH prior to anaesthesia is the best way to avoid an MH reaction during anaesthesia. Some patients do, in tissues of mesenchymal origin, exhibit stigmata typical of MH. While some are perfectly healthy, others complain of: ptosis and strabismus in childhood; kyphoscoliosis or lumbar lordosis; club foot, various kinds of hernias (inguinal, hiatus, umbilical); joint hypermobility with occasionally repeated joint dislocations; winged scapulae; undescended testicle; calcium stones in ureter or gall bladder; poor dental enamel and misshapen and misplaced teeth. Some patients exhibit skeletal muscle hypertrophy that is occasionally asymmetrical. Less often, hypertrophied muscles are interdigitated with atrophic muscles, rarely taking the form of overt arthrogryposis which may progress to generalized muscle weakness and wasting. A few MHS patients are afflicted with mild forms of Duchenne's muscle dystrophy, limb girdle muscular dystrophy, or central core disease.[17] The latter may begin in childhood or young adulthood. Skeletal muscle cramps that range from mild and infrequent to continuous and incapacitating, are the dominant symptoms. These cramps are usually worse in the winter, are relieved by going to warmer climates, but then recur shortly after the return to cold Canadian weather. Patients with a combination of unexplained muscle cramps, aches or pains, with or without joint pains, and a high CK, merit further investigation for the MH trait.[2,6,7,13,18]

CK measurement

Repeated serum CK measurements are worth doing, but one must never rely on a serum CK value alone to make a diagnosis of MH. In about 60 per cent of MHS patients, serum CKs are normal at least some of the time. In ten per cent of normal individuals, serum CKs are elevated. Within a given individual, serum CK levels are not reproducible. In MHS individuals, rest produces a greater reduction in CK levels than in normal persons. Conversely, exercise produces a greater elevation of serum CK values in MHS than in normal subjects. Elimination of the effect of exercise (or its lack) in serum CK levels necessitates constant exercise levels for several weeks before blood sampling. This is very difficult to achieve. Moreover, many other muscle damaging conditions that are unrelated to MH also elevate the serum CK, for example: hypothyroidism; paranoid schizophrenia; recent neurological injury; myocardial infarction; major skeletal muscle trauma; other myopathies; or chronic alcoholism. It should also be noted that serum CK levels are higher in Blacks and Orientals than in Caucasians.[18,19]

Muscle biopsy

At present, reasonably certain diagnosis can only be made by means of a muscle biopsy. The most widely accepted test performed on the excised muscle is the caffeine-halothane contracture (CHC) test (Figure 3).[5] The amount of muscle needed is much more than that required for microscopic examination only. Carefully dissected muscle fascicles are subdivided into small strips and mounted isometrically in baths of Krebs Ringer solution. The lower end of each strip is secured to the electrode frame while the upper end of the muscle is tied to a force displacement transducer enabling changes in muscle tension to be recorded on a polygraph. The strips are stimulated for two milliseconds once every five seconds at supramaximal twitch tension voltage and bubbled with carbogen (95 per cent oxygen and five per cent carbon dioxide). Incremental doses of caffeine are added directly to the bath and halothane, usually 1 vol%, is bubbled into the bath via the carbogen line.

The parameter upon which the test depends is resting tension (contracture). Twitch tension (contraction) is measured to confirm that the muscle strip is alive and well and to simulate the normal *in*

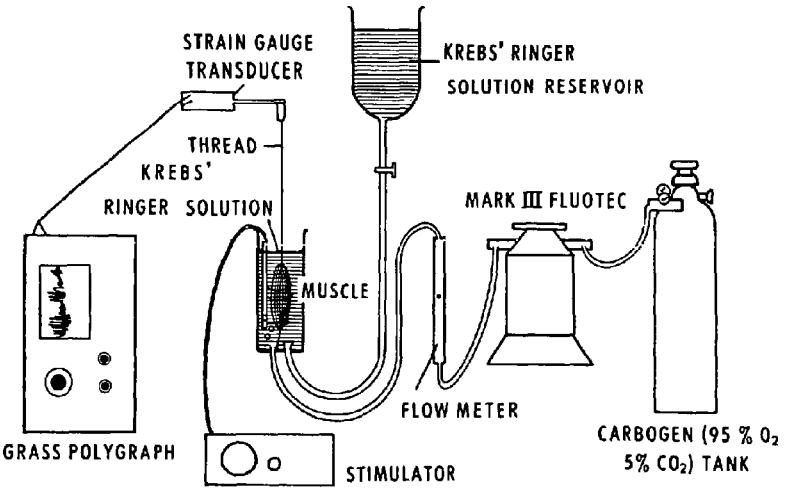

FIGURE 3 Experimental method for isolated isometric muscle twitch tension and contracture study.

vivo innervation of the muscle. In normal muscle, halothane does not increase resting tension but in severely affected MH muscle, 1 vol% halothane alone induces a contracture of several minutes duration. This is the most specific and least sensitive part of the CHC test. In muscle somewhat less severely afflicted with the MH trait, halothane contractures are absent but in both the absence and the presence of 1 vol% halothane, a lower than normal dose of caffeine is required to raise the resting tension of the muscle by 1.0 gram. This value is known as the "caffeine specific concentration" (CSC) in the absence of caffeine, and "caffeine specific concentration – halothane" (CSC-H) in the presence of halothane. Additionally the ascending portions of the caffeine contractures in MHS muscle are steeper, while the rate of fatigue of each contracture is more rapid than in normal muscle strips. The latter difference, due to greater fatiguability of the MHS muscle strips, increases as the dose of caffeine rises. Furthermore, while normal muscle lives for about 24 hours in the Krebs Ringer bath MHS muscle survives only five to seven hours. In very mildly afflicted MHS muscle caffeine contractures are absent, CSCs are normal but CSC-Hs are in the MH range. CSC-Hs are, therefore, the most sensitive but least specific part of the CHC test. The CSC and the CSC-H are calculated by plotting each caffeine contracture curve on semi-log paper. A horizontal line is then arbitrarily drawn at the one gram tension level. The point of intersection of this line with the caffeine contracture curve yields the CSC or CSC-H. The lower the CSC or CSC-H the more strongly positive the patient is for MH. The dividing point between MHS and normal in the absence of halothane is, in our laboratory, about 4.0 mM caffeine and in the presence of halothane about 1.0 mM caffeine.[15]

Other tests for MH performed on the excised muscle include the caffeine skinned fibre tension test, the ATP depletion test, radioactive calcium uptake test and microscopy. Details of the methodology of these investigative procedures are given in references 15, 20–22. While complimentary to the CHC test none are sufficiently reliable to be used as sole diagnostic tests.

Platelet and lymphocyte tests

Recently, we have been attempting to develop a non-invasive test to diagnose, or at least screen for, malignant hyperthermia. Since MH appears to be a widespread membrane defect and since platelets are really floating muscle cells, we commenced our investigative endeavours utilizing platelets, but found the problems of isolation of these cells difficult to overcome because patients persisted in taking medications such as aspirin, in spite of instructions to the contrary. Additionally, with all platelet tests we

assessed (caffeine inhibited aggregation, halothane induced acceleration of conversion of high to low energy nucleotides, and halothane and caffeine triggered shape changes), the incidence of false positive and false negative results was unacceptably high in our hands and the differences in mean values between normal and MHS subjects were either modest or absent.

We were persuaded, therefore, by Dr. Amira Klip of the Hospital for Sick Children in Toronto, to try the quin-2 method on lymphocytes. Quin-2 is a quinolene derivative that acts as a fluorophor. Its parent compound enters the lymphocyte where it is converted into negatively charged quin-2. Because of these negative charges, it is trapped within the cytoplasm where it binds almost exclusively to calcium to form a fluorescent product that can be measured in a spectrofluorometer to give the molar concentration of cytoplasmic calcium. In normal patients, the addition of halothane produces no significant increase in myoplasmic calcium, while it does do so in MHS patients whose muscle has developed contractures in the presence of halothane alone. In the absence of halothane, there are no significant differences in the calcium concentration between normal and MHS lymphocytes whereas a highly significant difference between normal and MHS lymphocytes exists in the presence of halothane. This test, therefore, may, with further refinements, prove to be a useful screening test for the more severe variants of MH. Much further work remains to be done, however, to confirm our preliminary results.

Elective management

Counselling

On the basis of the above investigations each patient who has been shown to possess the MH trait is issued with a Medic Alert bracelet which reads as follows:

Malig.
Hyperthermia
No Potent Inhal.
Anes. Agents or
Muscle Relaxants

Each of these patients is also issued with a card to be carried in his/her wallet that reads:

"Do not give: potent inhalational anaesthetics, quaternary amide muscle relaxants (okay pancuronium) amide local anaesthetics, cardiac glycosides, quinidine, parasympatholytics, sympathomimetics, tricyclics, MAO inhibitor, calcium salts. Safe drugs: ester local anaesthetics, narcotics, barbiturates, depressant tranquilizers, nitrous oxide, sympatholytics, parasympathomimetics, hormones and chemotherapeutics."

One must stress to the patient the need to wear the bracelet at all times. All uninvestigated individuals belonging to MHS families should also wear Medic Alert bracelets, particularly if they possess any of the stigmata of the MH trait and/or have elevated serum CKs.

The patients are asked to read a booklet* entitled "A Guide to Malignant Hyperthermia" which is written in layman's language and answers many of their questions and apprehensions. Families are counselled regarding the genetics and nature of MH, modification of life style, drugs and anaesthetic techniques that are safe for them during anaesthesia and the need for detailed preoperative visits with their anaesthetists. They also are invited to attend a yearly seminar held by the Malignant Hyperthermia Association – a patient self-help group. This seminar conducted by patients for patients, provides much support and information extremely useful to MH families.

Conduct of anaesthesia

When known or suspected MHS patients require anaesthesia they are pretreated with dantrolene. This drug,[23] related to diphenylhydantoin, acts by preventing (probably indirectly) the release of calcium from the skeletal muscle SR. When should dantrolene be given? In many centres, dantrolene is usually prescribed before each and every elective anaesthetic of a known or suspected MHS patient. The required dose of 2–4 $mg \cdot kg^{-1}$ is usually given intravenously over the last one to four hours prior to anaesthesia. Further amounts are given by the same route during and after the procedure. As intravenous dantrolene is both expensive and injurious to veins, an alternative method is to pretreat the patients for

*Available for purchase ($4.00) from the Malignant Hyperthermia Association, 2 Bloor Street West, Box 144, Toronto, Ont., M4W 3E2. 416-447-0052.

TABLE Contents of MH emergency trolley

Dantrolene sodium
Procainamide
Verapamil
Propranolol
Chlorpromazine
Sodium bicarbonate
Mannitol
Furosemide
Potassium chloride
Regular insulin
50% Glucose
Lactated Ringer's solution
Normal saline
Blood IV tubing
CVP lines
Arterial lines
Angiocaths
Duodenal tubes
Rectal tubes
Urinary catheters and bags
Peritoneal dialysis tubing and equipment
Plastic bags and twist ties for ice
20, 10, 5 and 2 cc syringes
#18 and #21 needles
Test tubes for muscle enzymes, electrolytes, blood sugar, urea nitrogen and lactate
Blood gas syringes
Temperature and oximeter probes and EKG electrodes
Water bath (one man life raft)

three days with oral dantrolene 4–6 mg/kg/day in four divided doses. Since we have biopsied about 1300–1400 MHS patients without dantrolene pre-treatment and all these patients are alive and well, we question the need for dantrolene in every case. At present, we are adopting a middle course by giving dantrolene if: the patient is very apprehensive; the surgery is going to be very long and injurious to muscles; the anaesthetic gas machine cannot be guaranteed to be absolutely free of inhalational anaesthetic vapours; the anaesthesia or the surgery are likely to be associated with a reduction in perfusion of the tissues or with some abnormality of the blood gases; or in an awake procedure during which the patient may be suffering some apprehension as in dental or obstetrical anaesthesia, particularly if an amide local anaesthetic agent is contemplated. A few cases of MH have been reported after pre-treatment with dantrolene, but in all, the dose has been inadequate. None have been observed when the loading dose has been at least 4 $mg \cdot kg^{-1}$. Postoperatively, the patient can be weaned off dantrolene in any convenient way over a three-day period. Patients being treated with oral dantrolene should be warned about its side effects: weak, rubbery muscles; uncertainty of location of the feet in space, making walking up and down stairs precarious; dizziness and double vision; a sensation of the eyeballs and tongue being swollen; dysarthria; nausea; occasional vomiting; epigastric cramps; diarrhoea; and impotence. Liver function tests should be repeatedly monitored although the early reports of dantrolene induced hepatitis have not been confirmed by later prospective studies.[7,23]

The night before surgery, we usually start an intravenous (IV) with lactated Ringer's solution with five per cent glucose. The reason for this particular IV formulation is that vasopressors or parasympatholytics are contraindicated and so the only way of preventing a fall in blood pressure is to ensure that the patient's vascular bed is well filled with a high osmotic solution before commencement of surgery. Lactate Ringer's solution in five per cent glucose has the greatest osmotic force of all electrolyte IV solutions presently available. To inhibit apprehension, the patient is premedicated two hours preoperatively with either diazepam or a shorter acting benzodiazepine such as oxazepam or lorazepam given orally or sublingually and then one hour preoperatively with a narcotic such as pantopon. No belladonna alkaloid is given.

In the operating room, a trolley which has every anticipated drug and piece of equipment needed to treat an MH reaction is available (see Table). At least 36 vials of dantrolene *must* be on this trolley. To date, the largest dose of dantrolene needed to successfully treat a patient in the initial phases of a MH reaction has been 100 vials. Therefore, 36 (the minimum number sold by the manufacturer, Norwich-Eaton Pharmaceuticals) is not an unusually large amount to have immediately available in the operating room.

One hundred pounds of ice should be in the operating room throughout the procedure. The patient should be placed on a cooling/heating blanket with the temperature control set to "automatic" at 37° C. Unless a reaction develops, the machine will be warming the patient throughout most of the procedure to prevent hypothermia. This is necessary since allowing the temperature to drop during the operation leads to shivering in the recovery room, with attendant chances of a stress-induced reaction. Hypothermia can also be retarded

by means of an inspired gas humidifier/heater. An electronic axillary temperature probe is installed before induction and a nasal temperature probe is inserted immediately after induction.[3,6–8,11,13,24,25]

Before commencement of anaesthesia, a blood pressure cuff and oximeter are attached to the patient and blood for muscle enzymes, electrolytes and venous blood gases are taken. Venous blood gases are more valuable than arterial blood gases, because blood coming from muscle alters first, rather than blood coming from the lungs. An end tidal CO_2 monitor is placed at the distal end of the anaesthetic breathing circuit. The anaesthetic gas machine should have no vaporizers on it, since vaporizers even when shut off frequently leak significant amounts of vapour into the inspired gases.[3,6–8,11,13,24,25]

If the procedure is not a muscle biopsy, the patient is induced with Innovar 0.5 $ml \cdot kg^{-1}$, a sleep dose of thiopentone and pancuronium (or other synthetic non-depolarizing skeletal muscle relaxant) and is intubated in the normal way using five per cent cocaine spray for anaesthesia of the vocal cords. Anaesthesia is maintained with pancuronium and any narcotic of choice. At the end of the anaesthetic, pancuronium is not reversed as both atropine and neostigmine should be avoided in MHS patients. The patient is taken to the recovery room and there ventilated until adequate respiration spontaneously returns.

If the procedure is a muscle biopsy, we do not give thiopentone or pancuronium because we have found that these agents interfere to some extent with our diagnostic tests. Rather, the patient is induced with nitrous oxide and oxygen 6:4 litres per minute for two minutes. Then 0.05 $ml \cdot kg^{-1}$ of Innovar is given IV very slowly. After another minute, a sleep dose of diazepam is infused. The patient is then hyperventilated by mask for two minutes, the vocal cords are sprayed with five per cent cocaine and the trachea is intubated with a tube that is at least one size smaller than normal because as the cords are not relaxed the aperture between them is correspondingly reduced. To assist intubation through the unrelaxed vocal cords, all types and sizes of laryngoscope blades and introducers should be at hand. The incidence of laryngospasm at the time of induction is higher in those with than in those without MH. This is best overcome with gentle pressure exerted by an endotracheal tube fitted with an aluminium introducer.

Anaesthesia is maintained with nitrous oxide and oxygen 6:4 liters. Hyperventilation throughout the anaesthetic is essential since it has been shown that in MHS pigs elevation of CO_2 (in the absence of triggering drugs) can induce hyperthermic reactions.[26,27] If necessary, further doses of fentanyl can be given but this is usually unnecessary since the surgery has generally been completed before the induction drugs have worn off.

At the end of the anaesthetic, the patient is ventilated with 100 per cent oxygen, reversed with naloxone and sent to the recovery room. There, if respiration is still inadequate, more naloxone, and perhaps physostigmine, may be given to ensure adequate ventilation. All vital signs, in particular temperature, are monitored every five minutes. The patients remain in the recovery room for at least four hours or until all vital signs are normal, whichever is the longer. After return to the ward, vital signs are measured every hour until late evening, and then every four hours for the next 24 hours.

To summarize, safe drugs for the anaesthesia of MHS patients comprise: nitrous oxide, narcotics, barbiturates, neurolept analgesics, synthetic non-depolarizing muscle relaxants such as pancuronium, atracurium, alcuronium and vecuronium. In small volume amide local anaesthetics appear to be safe but until their safety is proved more conclusively, it is probably wiser to avoid large volumes of amide local anaesthetics in MHS patients.[3,6,7,13,25]

Non-anaesthetic problems

Dantrolene is occasionally also used in the therapy of muscle cramps, stiffness and aches or pains associated with MH. In teenagers among whom such problems are usually associated with competitive sports, one 25 mg capsule may be prescribed before commencement of the exercise and one shortly after its termination. In middle aged persons suffering from chronic muscle or joint pain, dantrolene must be taken daily. To minimize side effects, the starting dose should be no more than 25 mg twice a day for at least a week. Then if tolerated and if pain is still not controlled, the dose may be increased by 25 mg per day over one to four weeks. Before commencing dantrolene therapy the patient must be advised in detail about the side

effects of this drug. The severity of these varies considerably from patient to patient. Interestingly, in our experience, the more severe the muscle pain, the more positive the CHC test for MH, and the more fulminant the MH reaction, the less severe are the side effects of dantrolene.

In families with a known history of stress-induced MH reactions it is advisable for each member to have on hand a small supply of dantrolene and chlorpromazine for use in an emergency. Patients should be counselled in family groups regarding recognition and management of stress-induced reactions occurring in themselves or their relatives.

Emergency management

Until a simpler, cheaper non-invasive test has been developed, inadvertent cases of MH will inevitably occur. Early recognition of developing signs is, therefore, essential. This can only be done if the anaesthetist maintains a high level of vigilance and closely monitors *all* patients undergoing anaesthesia. Frequent monitoring of heart rate, blood pressure, electrocardiogram, end tidal CO_2, oximetric capillary SaO_2, skin circulation and colour, blood colour, muscle tone and temperature are vital. Temperature must be measured electronically. Tempi-Strips should not be used since they are highly inaccurate and give readings far below those recorded by electronic means. Skin temperatures should be measured only within skin folds or clefts such as the axilla, where the recorded value is a reflection of underlying muscle temperature. This is because in the early stages of an MH reaction temperature of exposed areas of the skin may actually fall because of intense constriction of skin blood vessels.[3,6,7,13,24,26]

The first, and by far the most important treatment, is to stop the triggering drugs immediately. If it is vital that surgery continues, this can be safely done with any desired combination of narcotics, tranquilizers and nitrous oxide, but triggering drugs such as halothane and succinylcholine must be instantly stopped. All rubber tubing and soda lime must be replaced with new and unused tubing and soda lime. Ideally, the entire gas machine should be changed for one which is vapour-free. The patient should be hyperventilated at volumes of at least three to five times the Radford nomogram values to remove the excess CO_2 that is being produced in the muscles. Frequent measurements must be made of: blood gases, both venous and arterial; all serum electrolytes (sodium, potassium, chloride, calcium, phosphate and magnesium) and muscle enzymes (CK, lactic dehydrogenase (LDH), glutamic oxalic transaminase (GOT), glutamic pyruvic transaminase (GPT), hydroxybutyric dehydrogenase (HBDH); and aldolase); blood glucose; lactate and urea nitrogen. Sodium bicarbonate is given to correct the metabolic acidosis about halfway toward normal. Further correction appears to lower the survival rate from fulminant reactions.[3,6,7,13,24,25]

The drug of choice for the initial correction of the reaction is dantrolene. This agent is highly efficacious if given early.[23,28] Initially, it is given by bolus injection until reduction of heart rate, muscle tone and temperature occur. This initial dose ranges from $1-10\,mg\cdot kg^{-1}$ given at a rate of $1\,mg\cdot kg^{-1}\cdot min^{-1}$ and can be repeated after a fifteen minute pause if advisable. Otherwise, an IV infusion should be administered at a rate of $2-10\,mg\cdot kg^{-1}$ over each four-hour period. Further boluses may be necessary if, as not infrequently happens, the reaction recrudesces. Water to reconstitute dantrolene must be bacteriostatic agent free and the mixture must be thoroughly shaken for 2–3 minutes. Each vial contains three grams of mannitol. Since many vials may be given, the mannitol given in conjunction with dantrolene may become substantial and so must be subtracted from the total mannitol dose.[23,28] Also in each vial is enough sodium hydroxide to bring the pH to 9.5 and it is this high pH which is so injurious to veins. Resultant thrombophlebitis can be partially prevented by simultaneous and subsequent treatment with persantine.

Mannitol and furosemide should be given to prevent acute renal failure. Mannitol has the advantage of also correcting the muscle and cerebral oedema that develops and furosemide also helps to correct the sodium overload that is iatrogenically induced by use of large amounts of sodium bicarbonate.

Arrhythmias are best corrected with procaine or procainamide. The dose should not exceed $7\,mg\cdot kg^{-1}$ because during a MH crisis the myocardium is already compromised. Further reduction of

the myocardial myoplasmic calcium may fatally impair myocardial contractility. Verapamil can also be used for the same purpose but never at the same time as the dantrolene since together these drugs seriously reduce blood pressure. Repeated injections of 1.0 mg propranolol (0.015 $mg \cdot kg^{-1}$) may assist in lowering the heart rate.

Frequent measurements of serum potassium (every 15 minutes) are absolutely vital – first to detect early serum potassium elevation and then the subsequent low serum potassium. The former is treated with regular insulin in 50 per cent glucose while the latter is managed with IV potassium chloride, the doses of which may have to be very large and prolonged.[3,6,7,13,24,25]

Drugs of marginal value are barbiturates, narcotics and antipyretics. Chlorpromazine, however, produces a very substantial increase in survival rate. This is probably because it corrects peripheral vasoconstriction, thereby increasing heat loss and also because it reduces heat production through inhibition of shivering and of non-shivering thermogenesis in the mitochondrial electron transport chain and by reversal of calmodulin stimulated phosphodiesterase activity.[25] The efficacy of chlorpromazine in treating MH reactions supports the thesis that MH and neuroleptic malignant hyperthermia are not identical.[29]

If the temperature has already risen, the patient will require cooling with a cooling blanket and/or an ice water bath. Hopefully, now with earlier diagnosis and dantrolene treatment, marked cooling should not be necessary. The reaction should be diagnosed before the need arises for internal cooling with cold solutions in the stomach, rectum or abdominal cavity. We are able to keep virtually all our MHS pigs alive during reactions without the aid of any cooling but rather with dantrolene and sodium bicarbonate therapy alone. If, however, the reaction is diagnosed late, then these desperate measures plus cooling with cold IV solutions and even extracorporeal cooling may still be necessary.[2,3,6–8,13,24,25]

Drugs which should never be given during a reaction because by one mechanism or another they all elevate myoplasmic calcium include: amide local anaesthetics, cardiac glycosides, calcium chloride, belladonna alkaloids and vasopressors. Use of any of these agents raise the mortality rate to over 90 per cent.[6,7,13,24,25,30]

Finally, the patient should never be moved (from the operating room to the recovery room or the intensive care unit, or from a community hospital to a teaching hospital) until the reaction is completely under control, because even minor physical stimulus appears to stimulate recrudescence of the reaction in an especially lethal form characterized by arrhythmias. MH is like a smoldering underground fire and while it may superficially appear to have subsided, stopping dantrolene too soon may well permit recurrence in probably a worse form than initially sustained. If the reaction, therefore, has been fulminant, vigorous monitoring and treatment must be continued for several days. Even the smallest hospitals must be prepared for such an eventuality. On the other hand, if the diagnosis has been made immediately after induction and treatment has been immediately begun, the patient may well be fully recovered the following day.

Conclusion

Malignant hyperthermia is potentially lethal. Nevertheless, because of improved awareness and treatment, mortality has dropped from 86 per cent in the 1920s to seven per cent in the 1980s.[30] Individual consideration of the seven per cent of patients who died of MH reactions in the 1980s reveals serious errors of management in all. Appropriate treatment of malignant hyperthermic reactions should be followed by 100 per cent survival.

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